APRIL 1954

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

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ANNUAL REPORT OF THE PRESIDENT

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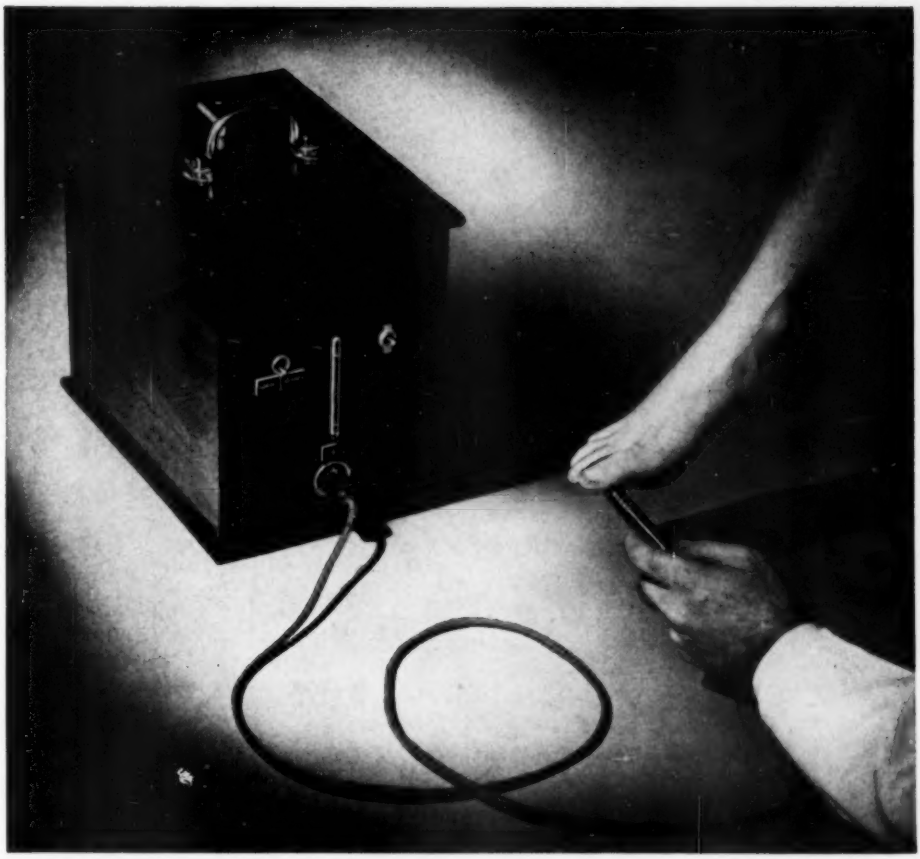

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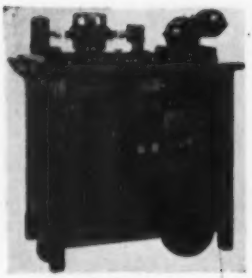

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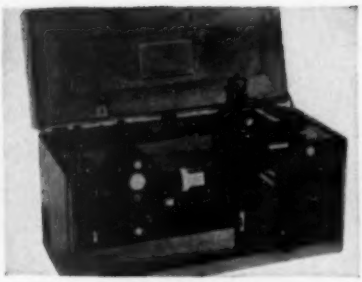

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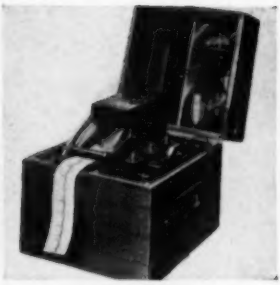

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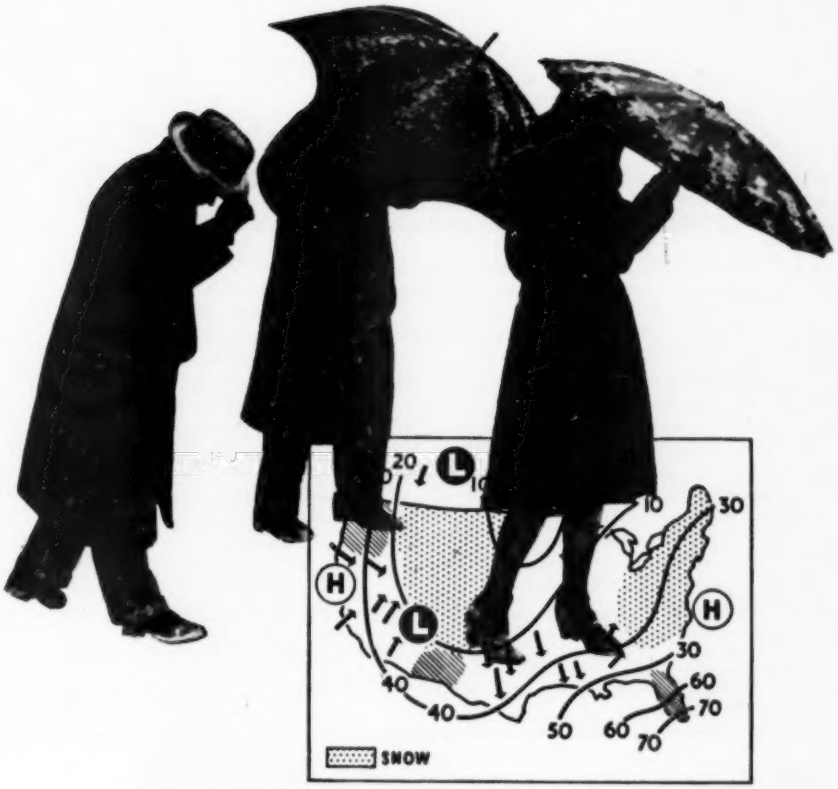

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1. Breese, B.B.: J.A.M.A. *152*:10 (May 2) 1953.
2. Stollerman, G.H.; and Rusoff, J.H.: J.A.M.A. *150*:1371 (Dec. 20) 1952.
3. Tidwell, R.A.: Paper read before Annual Meeting, Washington State M. Assoc., Seattle, Sept. 12-16, 1953.

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[1]Zink, O. C.: Routine Clinical Experiences Using UROKON 70% in Intravenous Urography (Private Report dated May 12, 1952).
[2]Nesbit, R. M. and Nesbitt, T. E.: Experiences with High Concentration UROKON for Pyelography. Univ. of Mich. Med. Bull. *18*:225 (1952).
[3]Barry, C. N. and Rose, D. K.: UROKON SODIUM 70% in Excretory Urography, J. Urol. (to be published).

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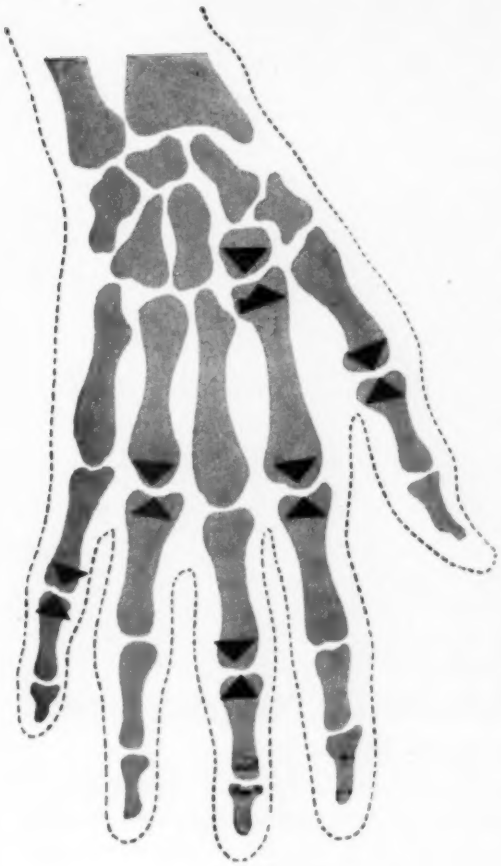

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1. Grayzel, H. G., Heimer, C. B., and Grayzel, R. W.: New York St. J. M. 53:2233, 1953.
2. Heimer, C. B., Grayzel, H. G., and Kramer, B.: Archives of Pediatrics 68:382, 1951.
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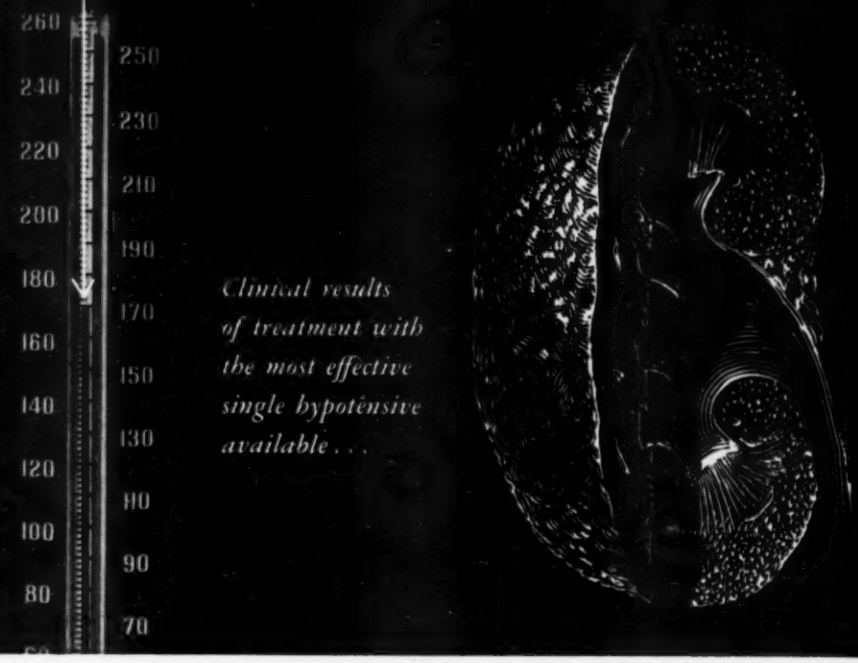

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1. Moyer, J. H.; Miller, S. I., and Ford, R. V.: J.A.M.A. *152*:1121 (July 18) 1953.
2. Moyer, J. H.; Snyder, H. B.; Johnson, I.; Mills, L. C., and Miller, S. I.: Am. J. M. Sc. *225*:379 (April) 1953.

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 30, NO. 4 APRIL 1954

ANNUAL REPORT OF THE PRESIDENT

ALEXANDER T. MARTIN

President, The New York Academy of Medicine

My report to the Fellowship of the Academy for the year of 1953 is one, not only of progress but one of great accomplishment, and a balanced budget. This latter significant achievement is due in large measure to the husbanding of our resources and wise expending by our Treasurer, Dr. Shepard Krech, the guidance and wisdom of the Trustees and Council, the able administration of our Director, Dr. Howard R. Craig and the faithful service of our Comptroller, Mr. Arthur A. Eberle.

The Academy functions through its Standing Committees and at the heart of it all stands the Library with its Rare Book Room. We are justly proud of all these and of the services they render. I shall attempt to summarize the activities of these committees.

THE COMMITTEE ON PUBLIC HEALTH RELATIONS has dealt with a multiplicity of matters pertaining to public health under the Chairmanship of Dr. George Baehr and Dr. Harry D. Kruse as Executive Secretary.

The two public health lectures were outstandingly successful and

* Presented at the Annual Meeting of The New York Academy of Medicine, January 7, 1954.

drew large and appreciative audiences. First, the Hermann M. Biggs Memorial Lecture was presented as a Symposium on Poliomyelitis, and the speakers were investigators who had recently made distinguished contributions to the intensive efforts to conquer this disease.

Second, the A. Walter Suiter Lecture endowed by a legacy from a Fellow of the Academy, was also in the form of a symposium. The subject was "The Influence of Environment on Mental Health" and the speakers were two Professors of Psychiatry, Dr. John C. Whitehorn of Johns Hopkins and Dr. Fredrick C. Redlich from Yale.

The Suiter lecture was given against the background of a Conference on the Etiology of Mental Disease sponsored by the Committee and bringing into relief the convergence of viewpoints on the etiology of mental disorders. Forty-five psychiatrists and psychologists, with five from abroad, participated in the conference which lasted two days.

Housing: New York's continuing housing problem has engaged the attention of the Committee on Public Health Relations for several months during the year. From their many deliberations, there has developed a report which "suggests that machinery be found for the coordination of the efforts of the many groups concerned with housing." Although the Committee was aware that its area of competence was restricted to the effects of housing on health, it was obliged to recognize that the problem of providing proper housing in New York City is basically economic. It pointed out that ill-health is costly to the individual, his family and the community, that good health is purchasable and that the ever-rising level of public health has brought with it economic gain. Thus, health and social welfare are inseparably intertwined. If the economic need can be met, the health benefits will undoubtedly follow.

The Nursing Shortage: Cognizant of the critical shortage of nursing services in New York City, the Committee on Public Health Relations was host to a series of conferences attended by representatives of the leading organizations in the state concerned with nursing problems. The Committee recognized the need of two state-wide surveys, and a letter proposing this project was sent to the Interdepartmental Health Council headed by State Health Commissioner Herman E. Hilleboe. In cooperation with other health, educational and nursing organizations, the Committee supported legislation to lower the age for the licensing of practical nurses to 18 years.

Maternity and Newborn Services: At the request of the Department of Health, the Committee received a proposed revision of Section 110 of the Sanitary Code relating to hospital service for maternal and infant care. The Committee was of the opinion that many of the resolutions were too rigid for incorporation in a mandatory code and should instead be put into the form of standards. The Assistant Commissioner of Health in charge of maternal and child health services expressed great appreciation of the Committee's work in helping to bring Section 110 into agreement with recent developments in obstetric and pediatric practice.

Commissioner of Hospitals: At the request of the Mayor-elect, the Committee was asked to advise as to qualified hospital administrators for the position of Commissioner of Hospitals. A number of men experienced and prominent in the hospital administrative field in various parts of the country were recommended to him.

Air Pollution Control: At the invitation of the newly established Department of Air Pollution Control, the Committee in expressing an opinion on certain proposed revisions in the Rules and Regulations of the Department urged greater provision for research and suggested that the Department develop a program of education directed first, toward the community as to possible health hazards and second, toward industry as to its responsibilities in the prevention of such hazards.

Conferences with Medical Social Workers: A conference was held with representatives of the North Atlantic District of the American Association of Medical Social Workers and a joint committee established with a view to the establishment of a formal relationship, through which the association might strengthen its program. The social workers expressed their desire, first, for an evaluation of the services their profession has to offer; second, for an interpretation of these services to the community; and third, for advice on specific problems, such as tuberculosis among the Puerto Rican population, care of the chronically ill, and the social aspects of tropical disease. It was suggested that representatives of the visiting nurses and public health nurses be brought into the group.

Commission to Study Licensure in the Healing Arts: The Committee's support was enlisted by the Medical Society of the State of New York to oppose the licensure of certain practitioners in the healing arts, specifically the chiropractors who were making repeated efforts to achieve licensure. A comprehensive study was recommended and the authorization of a commission was asked for. A Bill was introduced in

the Senate but this Bill was never reported out of committee. As for many years past, the chiropractors of the State again pressed for the passage of a licensure law. This year the Bill appeared to have a good chance of success but was defeated in the Senate.

THE COMMITTEE ON MEDICAL EDUCATION has had an unusually good year under the Chairmanship of Dr. Franklin M. Hanger with Dr. Robert L. Craig as Executive Secretary. Outstanding in the accomplishments of this Committee were the preparation and presentation of the Twenty-Sixth Annual Graduate Fortnight on "Disorders of the Blood and the Blood-Forming Organs." The attendance was excellent, with over 8000 recorded admissions. Physicians and students of medicine came from distant points. The hospital clinics contributed much to the Fortnight. The wisdom of holding these clinics at the Academy in the second week is still to be evaluated. The Panel Sessions, increased in numbers, were very popular. The Scientific Exhibit was unusually fine, and it is unfortunate that this cannot be made a matter of permanent record. An experimental television program was given an initial trial. This demonstrated a device to restrict the reception of clinical programs to physicians only. Our Director and Dr. Paul Reznikoff participated in the program. The first award of the Harlow Brooks Medal was presented to Dr. Nathan Rosenthal at one of the evening sessions.

Upon the request of the New York Municipal Civil Service Commission, the Committee gave recommendations regarding educational qualifications for medical positions in the City Departments.

The Committee has reinstituted the Medical Research Forum.

The Monthly Panel Meetings on Therapeutics have replaced the Friday Afternoon Lectures and have been most successful and better attended.

The Committee on Medical Education arranges the scientific programs for the Stated Meetings. These are of a very high order but in the main are poorly attended, and we urge a greater support of the Fellowship. An attempt was made during the year to combine scientific sections, hoping thereby to increase the attendance but this has fallen short of expectations.

The Committee on Sections, composed of the officers of the twelve sections, has given significant service to the Academy. It is through the scientific sections that a majority of the Fellows have their closest con-

tacts with Academy activities. The section officers have done a splendid job in organizing the programs of papers, symposia, panel meetings and clinical demonstrations for their respective section meetings and are to be commended.

The Academy Bulletin continues to be a medical publication of high calibre, presenting many authoritative articles in various branches of medicine. It is widely read, quoted and abstracted both in this country and abroad.

The Committee on Medical Information has had a busy year and a productive one under the Chairmanship of Dr. Frank J. McGowan and Dr. Iago Galdston as Executive Secretary. Perhaps the most interesting and inspiring achievement was the Institute on Medical History held at Arden House at Harriman, New York, for two days. This occasion was distinguished by the participants and the program which was presented.

The Eastern States Health Education Conference was a particularly effective meeting in the series of annual meetings held for two days here at the Academy. The conference dealt with "The Sociology of Health Education." The transactions of the 1951 conference were published during the year under the title "The Epidemiology of Health," and have been reviewed most favorably both in the Americas and abroad.

The transactions of the conference on Panic and Morale were also published and the demand has exceeded the supply. A second conference on Morale is being planned by the Committee.

Other projected publications are being undertaken, thus bringing the activities of the Academy to a vastly larger audience both in the United States and abroad.

The Lectures to the Laity are now well established. The series this past year have not been confined to medicine but deal with the "Reciprocal Relations between Medicine and the other Disciplines." They have been given by a distinguished group of speakers.

The weekly radio programs of the Academy's post-graduate series "For Doctors Only" transmit to the physicians of Greater New York the best of the Academy programs.

The Bureau has received and handled over 13,000 inquiries with 2,500 coming from the Press. Thirty-five press releases were issued, covering the various activities of the Academy. One hundred and

seventy-one manuscripts were reviewed. This will give some idea of the very busy Bureau and activity of the Committee on Medical Information.

THE COMMITTEE ON ADMISSION under the able Chairmanship of Dr. Locke L. Mackenzie has rendered a fine service to the Academy and especial commendation is in order for their responsibility in maintaining the high standards of Fellowship.

THE LIBRARY. As has been mentioned previously, our Library is the heart of the Academy. It is under the guidance of the Library Committee under the Chairmanship of Dr. Samuel W. Lambert, Jr. The members have been well selected; for they are well-informed and alert to the Library's needs. The Library has taken on a new dress in the past year, and the restoration and reconstruction has cost us almost $300,000. Included in this is the cost of new stacks which were urgently needed for the more than 300,000 books which the Library now holds and which continues to be the second largest medical library in the country, second only to the Armed Forces Medical Library in Washington, D.C. Miss Janet Doe continues as our able librarian and the Academy is indebted to her and her staff for their loyal and efficient services. During the summer months, the library was closed for the moving of over 100,000 books into the new stacks and for another part of the year was closed for renovations. The completion of these was celebrated on May 21st by a large group of Fellows and friends.

The card catalogue has been expanded to nearly double its previous size and the classification system of the Armed Forces Medical Library has been adopted for the Academy library.

The Rare Book and History of Medicine Room has become a priceless possession. Hereafter, it will be known as the Malloch Rare Book and History of Medicine Room, memorializing Dr. Archibald Malloch, who died during the year. He was librarian for twenty-five years and was the founder of the Rare Book Room. The Library today is a tribute to his ideas and ideals, and it is proper that he should be so honored and remembered. It was Archibald Malloch's intent that the Rare Book Room, which now is captioned by his name, was not to be a mausoleum of old texts but a repository of all historical lore. In it are stored many priceless incunabula and manuscripts. Archibald Malloch built well and

wisely. He was one of those rare persons who was able to transmute his avocation into a vocation.

As has been stated, the library reconstruction was completed at a cost of about $300,000, providing five new floors of stacks, an additional floor for staff work, increased space allowing some 1,800 of our 2,600 periodicals to be on open shelves. New lighting has been installed in the Reading Room and the entire room re-decorated, as well as new lighting in the periodical room, the catalogue room and the work rooms for the staff. A new call system has been installed facilitating the flow of traffic around the reference desk in the catalogue room. The Academy acknowledges a debt of gratitude to all those both within and without the medical profession, who by their contributions made this restoration work possible.

Renovating of the ventilating system of Hosack Hall and Room 20 has already begun and estimates are being prepared for the re-lighting and sound-proofing of the Presidents' Gallery.

The new panel system of medical consultants to the Justices of the Supreme Court has met with great success. This was undertaken in cooperation with the Bench, the Bar Association, the County Lawyers Association and the Medical Society of the County of New York. The experimental period is almost ended and a report will soon be issued.

There has been an ever-increasing cooperation with voluntary and governmental agencies, such as the City Departments, the various Tuberculosis and Health Associations, the Cancer groups, the Heart groups and many others in various projects, such as conferences, radio and television broadcasts. These have served as media of communication by which knowledge has been diffused to both professional and lay groups. Many have contributed to these ends and have made the Academy a community institution, devoting itself to education and the public health.

We are happy to report to the Fellowship that the year closed with a balanced budget. Total expenditures amounted to $544,600. For this year of 1954, there will be an increase in the budget of $9,203, making a total budget of $553,803. The anticipated income this year is $524,600, and the anticipated deficit is $29,203. We would stress the need for continued and increased contributions, from individuals, business and industry. Special note is made that the Library, which is a free public medical library open to the general public, will expend $228,442. This represents about 41 per cent of the total budget.

The total assets of the Academy are $11,015,747 with invested funds of $7,392,629 and fixed assets and deferred charges of $3,623,118.

The immediate needs are: 1) an increased endowment by a million dollars to provide an additional $40,000 income to carry on the manifold activities; 2) a revolving publication fund of $100,000 to insure the publication of transactions of conferences and of studies prosecuted by the Academy and its staff; and 3) further funds to renovate and bring up to date the fabric of the Academy building, now twenty-eight years old.

Each year begins as a venture of faith and ends as a fulfillment of a hope. The past year has been no exception. We owe this in great measure to our Director, Dr. Howard R. Craig, who has been the guiding hand in all the Academy affairs. He has been wise where wisdom was needed and has been cautious where caution was needed. He has been a good moderator as well as a most able executive and administrator.

I wish to acknowledge the services of all the officers, the Trustees under the fine Chairmanship of Dr. Orrin S. Wightman and all the members of the Council, also the staff both at the executive and sub-executive level and of all the Fellows who have contributed of their services and time. And lastly, I wish to acknowledge the aid of those lay people and organizations who by their encouragement and help have supported the work of the Academy.

And now in its 108th year, the Academy goes forward and notes another year of progress and accomplishment. It is indeed a high honor and a great privilege to be associated with such an Institution and with those who make up its Fellowship.

BASIC MECHANISMS OF HEMOSTASIS*

MARIO STEFANINI†

Research Professor of Medicine, Tufts College Medical School,
Physician, New England Center Hospital, Boston, Mass.

THE ponderous literature on the subject of hemostasis could perhaps be considered a classical example of the infinite ability of the human mind for abstract speculation. For several years, the number of working theories of the hemostatic mechanism greatly exceeded and not always respected the confirmed experimental facts. In recent years, however, the revived interest in this field has led to an accumulation of new findings which has been almost too rapid for their orderly incorporation into a logical working pattern. As a result, we have rapidly gone from a state of "orderly ignorance" to one of "confused enlightenment," from which we have not emerged as yet. As new facts and new observations are sorted and critically evaluated, however, they begin to find a proper place and a concept of the hemostatic mechanism is beginning to shape which appears as complex as it is fascinating.

A normal hemostatic mechanism is a very important aspect of human survival. Small, repeated traumas of every day life continuously produce minor injuries to the vessels and, thus, the danger of spontaneous hemorrhage. "Extrinsic" trauma may, by severing vessels, cause bleeding which must be promptly controlled. Both functions require a perfect integration of a number of elementary mechanisms. The vascular wall must present normal resistance and contractility, the platelets and many factors which take part in the coagulation process must be normal in number or concentration, and in activity. Other mechanisms, such as fibrinolysis (which may play a role in limiting the undue extension of the fibrin clot within the vessel) and all the agents which bring about "organization" of the clot, recanalization of the vessel, etc. must also be normal. The very complexity of these mechanisms, then, creates many situations

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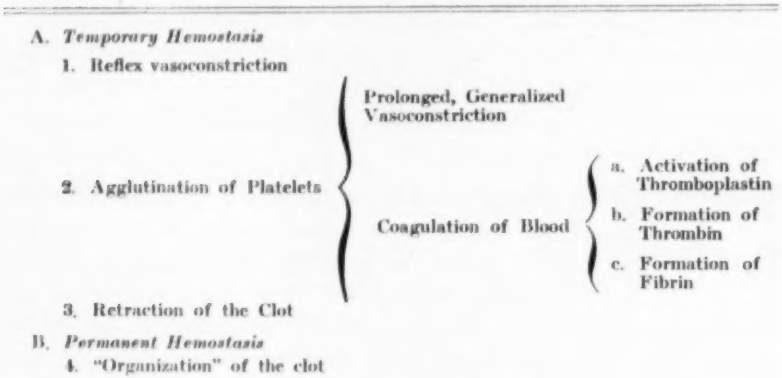
† Established Investigator, American Heart Association.

FIGURE 1—PHASES OF THE PROCESS OF HEMOSTASIS IN THE NORMAL MAN FOLLOWING INJURY



This scheme emphasizes the central role of platelets in the process of hemostasis. Platelets: (a) Supply the vasoconstricting agent; (b) Activate thromboplastin, thus initiating the coagulation process; (c) Determine clot retraction.

when hemostasis may become insufficient and bleeding may follow. The intricacies of the hemostatic process can probably be best illustrated by reviewing briefly the sequence of events following injury to a blood vessel. There is, of course, no uniform pattern. Absolute or relative lack of pressure within the lumen of the vessel greatly simplifies the hemostatic mechanism in the case of smaller capillaries and veins. The lumen collapses, the endothelial intimas come in contact and adhere, re-establishing the continuity of the endothelial lining. Thus platelet agglutination and fibrin formation may not even occur in many instances. Bleeding from the arterioles (the most common site of bleeding following "extrinsic" injury) is controlled by a more complex series of mechanisms (Fig. 1). Local, fleeting vasoconstriction caused by an axonic reflex promptly follows the injury to the vessel and the overlying structures. Its physiologic significance is not clear, although, by slowing the circulation, this mechanism may facilitate the accumulation of platelets along the vessel wall and at the site of injury. There platelets promptly agglutinate. In part they act by mechanically plugging the vessel wound. But far more important, however, seems to be their ability to release a series of agents which initiate and govern the following phases of the hemostatic process. The marked, prolonged, more generalized vasoconstriction

which follows platelet agglutination is apparently due to the release of serotonin (5-hydroxytryptamine), either directly or through a plasma-platelet interaction. This is a fundamental step in the hemostatic process since the consequent reduction of blood flow through the vessel wound greatly favors accumulation of thrombin and fibrin formation. Another platelet factor initiates blood coagulation, which is also accelerated by additional platelet constituents. The fibrin clot is finally formed; shortly afterwards it retracts, its size perhaps reduced by fibrinolytic agents. "Organization" of the clot, and recanalization of the vessel follow and very often a new normal endothelium soon lines the vessel in its entirety.

This short description of an hypothesis of the hemostatic process indicates the advisability of individual analysis of the various mechanisms: (a) the vascular mechanism; (b) the platelet factor; (c) the blood coagulation mechanism; (d) the autocatalytic mechanisms; (e) the anticoagulant factors; finally (f) the fibrinolytic mechanism. It should not be forgotten, however, that these various mechanisms are very closely integrated, as is clearly revealed by the study of the pathogenesis of bleeding in various types of hemorrhagic tendency. The single abnormality of one of the hemostatic mechanisms is not necessarily followed by bleeding, if all others are normal. Thus bleeding is moderate and may occur only following serious trauma or operative procedures in pseudohemophilia, congenital deficiency of prothrombin, labile factor, stable factor and fibrinogen, severe as the defect of the hemostatic mechanism involved might be. In many, better defined hemorrhagic syndromes, there is multiple involvement of hemostatic mechanisms. Thus, in some cases of Werlhof's disease, particularly of the acute variety, thrombocytopenia is accompanied by pronounced involvement of the vascular wall (polyarteritis).[1] In parenchymal liver disease, not only is the concentration of the various coagulation factors reduced, but vascular resistance is decreased, while plasma antithrombin titer and fibrinolytic activity are increased. Finally, some of the controlling factors of the hemostatic process may regulate more than one mechanism. A very interesting relationship is that of vitamin K deficiency to vascular fragility.[2,3] In Dicumarol intoxication, hypoprothrombinemia is accompanied by increased vascular fragility (and capillary bleeding is often found). Both abnormalities are promptly corrected by the administration of vitamin K_1. Also in parenchymal liver disease low plasma prothrombin activity and positivity of the tourniquet test are fairly well correlated,

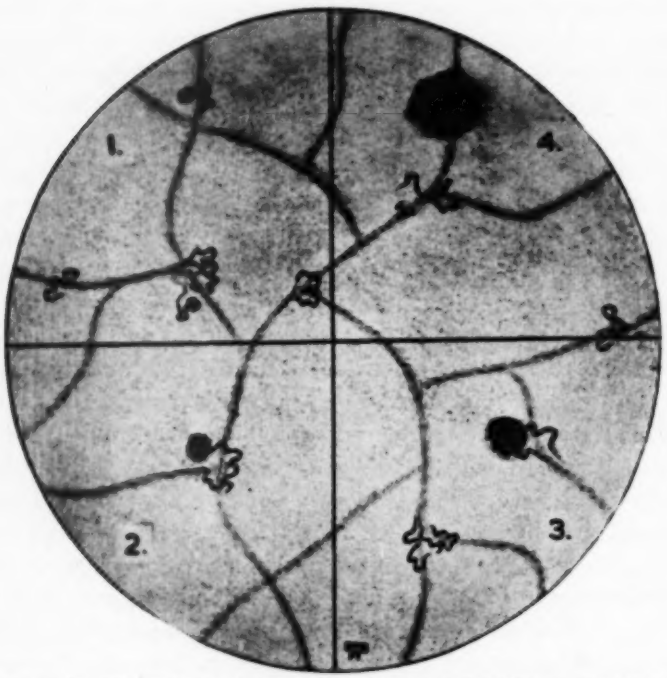


FIGURE 2—STAGES OF FORMATION OF A PETECHIAL HEMORRHAGE IN IDIOPATHIC THROMBOCYTOPENIC PURPURA — There is extravasation of blood (2-3) without apparent lesion of the capillary. Slow reabsorption of extravasated blood (4).

For permission to reprint, see note under Figure 3.

and both may be corrected by the administration of large doses of vitamin K. It may be argued with good reason, therefore, that the subdivision of the hemostatic process into individual mechanisms is probably unwarranted. It is, however, justified if one wants to understand the principal role and significance of each.

THE VASCULAR MECHANISM

The importance of the vascular mechanism of hemostasis is obvious in the control of the response of the vessel to trauma. It is probably equally important in the control of spontaneous bleeding, if one remembers that even marked thrombocytopenia or marked deficiency of blood coagulation factors may not be accompanied by bleeding when, as seen in hypoprothrombinemia, afibrinogenemia, etc., vascular resistance is

not impaired. On the other hand, vascular fragility may cause severe hemorrhagic manifestations although platelets and coagulation mechanism are normal. This situation is best illustrated by the severe bleeding which may follow a small trauma in patients with pseudohemophilia of the vascular variety. In this disease, deficient vascular contractility (prolonged bleeding time) represents the only demonstrable abnormality.

For all its importance, the vascular mechanism of hemostasis is very poorly understood. This is due to many reasons: (a) The evaluation of the status of vascular resistance and of the sufficiency of the response of the vessel to injury is left, at least for practical clinical use, to two very poorly standardized tests: the tourniquet test and the determination of the bleeding time; (b) the mechanism of formation of the elementary bleeding lesions is not entirely clear. Thus, it is thought by many that petechiae represent the result of extracapillary extravasation of red cells and white cells,[4] without demonstrable lesions of the vessel (Fig. 2). Their disappearance in a matter of hours, however, without any discoloration of the overlying skin does not support this contention and there is histologic evidence that petechiae, at least in some stages of their development, may represent aneurysmal dilatations of the capillary wall;[5,6] (c) the site where spontaneous bleeding occurs is also questioned. It may occur from the capillary loop,[5] or, more likely, from the meta-arteriole (terminal arteriole), particularly where collaterals are given out (Fig. 3). The second hypothesis has the support of extremely accurate experimental evidence collected with the direct study of the circulatory changes in the rat meso-appendix and also of data collected by the use of the capillary microscope, which will be described later. The importance of the meta-arteriole in the control of bleeding due to "extrinsic" injury is, on the other hand, obvious since control is achieved in great part by vasoconstriction and capillaries are now known to be devoid of contractile tissue.

There are various causes which may lead to spontaneous bleeding from the meta-arteriole or the capillary. "Spontaneous bleeding" is extravasation of blood from the vessel, due to the inability of the vessel to withstand the pressure within the lumen or to control promptly minor vascular injury inflicted by small traumata such as each of us meets in every day life (contraction of muscles under the skin, articular movements, etc.). The vessels may be *congenitally abnormal*, as presumably they are in hereditary hemorrhagic telangiectasia, vascular pseudohemo-

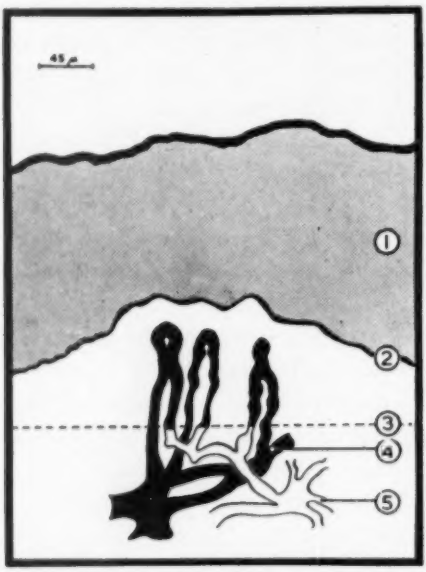


FIGURE 3—SITE OF PETECHIAL FORMATION*: the dotted line (3) indicates where petechiae form. The area in solid black is the one which can be seen under the capillary microscope.

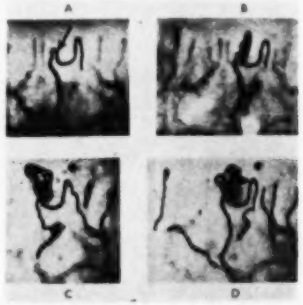
* (1) horny layer of skin; (2) malpighian layers; (4) first collecting venule; (5) terminal arteriole.
Figures 2 and 3 are from J. G. Humble,[4] in *Blood 4:69-75*, 1949. Reprinted by permission of the author and the publishers, Grune & Stratton, Inc.

philia, pulmonary hemosiderosis, idiopathic hematemesis and melena, etc. In such instance, bleeding is probably due to primary inability of these vessels to contract following trauma. Or the *permeability* of the vessels may be abnormally high. The capillary wall is composed of fibrillary membrane, a layer of endothelium and a "cementing" substance which unites the individual endothelial cells. Hyaluronic acid is an important constituent of the cementing substance and ascorbic acid is necessary for its synthesis. Spontaneous bleeding follows defect of the "cementing substance," however caused. Experimentally, bleeding follows when one applies hyaluronidase locally to vessels in the rat meso-appendix preparation.[7] Clinically, a defect of the "cementing substance" is found in scurvy. Finally, the *fragility* of the vessels may be higher than normal. This condition makes any minor trauma an important possible cause of severe bleeding.

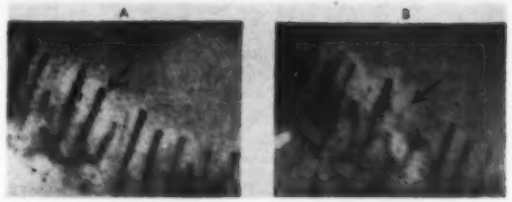
What changes in the vessels induce increased vascular fragility and spontaneous bleeding is not known at present. Little or no information is obtained with the histologic examination of the vessels, since, with the already mentioned exception of some cases of acute idiopathic thrombocytopenic purpura, no significant histologic lesion is detectable in most cases with hemorrhagic tendency. Fragmentary information has been obtained with studies "in vivo." As mentioned already, Humble[4] witnessed petechial formation in patients with hemorrhagic tendency with or without thrombocytopenia by the elegant technique of following changes in the visible capillaries of the nail bed under the experimental conditions of the tourniquet test. In all cases, hemorrhage occurred from the arterial end of the capillary loop (Fig. 3), where, as Landis[8] has demonstrated, the pressure within the capillary is the highest and the vessel suddenly dilates into the capillary loop. There was no demonstrable obliteration of the vessels during or after hemorrhage. Thus, inability to contract was of paramount importance in explaining the increased vascular fragility and the spontaneous bleeding when the intravascular pressure was elevated. Humble's findings on the mechanism of bleeding in hemorrhagic disease are very similar to those obtained by MacFarlane[9] with regard to the response to trauma of the capillary loop in various hemorrhagic diseases (Fig. 4). Methods such as used by Humble and MacFarlane are not without criticism. Thus, in MacFarlane's work, disappearance of the capillary loop was considered evidence of vasoconstriction. In fact, it may only have represented "skimming" or emptying of the capillary loop since the method visualized the contents and not the walls of the capillary. Figure 4/2 shows, to the left, a normal nail-bed field: some capillary loops are clearly defined, others less so, possibly due to "plasma skimming"; to the right, is a picture of what happens when the loop is damaged (by quartz needle puncture, in this case). The injured vessel disappeared from view (it did not reappear again for as long as one-half to two hours). At the height of vasoconstriction, this was so intense that the arterial end of the capillary loop could withstand internal pressures as high as 100 mm. Hg. It is not difficult to understand how this prolonged, intense vasoconstriction must have favored the clotting of blood within the loop. Figure 4/3 shows studies in patients with primary vascular defect (pseudohemophilia) as well as thrombocytopenia. The capillary loops often appeared distorted. In both instances little or no vascular contraction took place and bleeding con-

FIGURE 4—RESPONSE OF HUMAN CAPILLARIES TO INJURY.

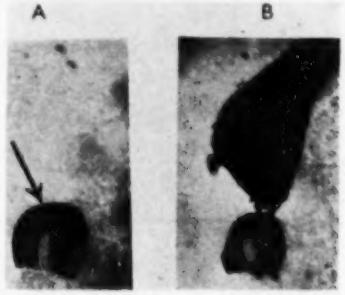
(1) Changing appearance of the capillary loops in normal human fingernail bed.
(After Parrisius; Deutsche Zeitschr F. Nervenheilk., 1921)



(3) Capillaries in a case of vascular purpura.
A—Capillary loops appear irregular and distorted.
B, C, D—No contraction of the loop immediately, 2′ and 5′ after injury blood is accumulating around the vessel.



(2) Normal capillary loops in human nailbed.
A—Normal capillaries.
B—Injured capillary loop has disappeared (contracted?).



(4) Capillaries in a case of hereditary hemorrhagic telangiectasia.
A—Greatly distended capillary.
B—No contraction of the loop after injury. Large hemorrhage.

Fig. 2, 3, 4 from MacFarlane,[9] Quart. J. Med., 1941. Reprinted by permission.

tinued for minutes, until finally arrested by outside pressure of the extravasating blood. A similar picture was found in congenital abnormalities of the vascular system, such as hereditary hemorrhagic telangiectasia (Fig. 4/4). In this condition also the capillary loop was greatly enlarged and distorted. Lesion by the needle was followed by large hemorrhage. Studies like those by Humble and MacFarlane, which have been repeated and confirmed by others, have been very fruitful in supplying information as to the role of vessels in hemorrhage and hemostasis.

Lack of vasoconstriction following trauma and poor contractility of the vessel may then be one of the important causes of spontaneous bleeding or of defective hemostasis after trauma. The pathogenesis of both abnormalities is not clear, with the exception, perhaps, of the thrombocytopenic states. The brilliant experimental work by M. B. Zucker,[10] confirmed in man by H. D. Zucker[11] by the painstaking method of studying histologically serial skin sections of thrombocytopenic patients, has done much to illustrate the role of platelets in vasoconstriction and vasocontractility. When, however, no platelet deficiency can be demonstrated, the vessel's permeability may be grossly abnormal or other factors controlling vasoconstriction may be deficient. This brings us to a short discussion of some other factors which may influence the response of the vessel to trauma or control spontaneous bleeding. Knowledge in this field is sorely inadequate.

As mentioned already, ascorbic acid is necessary for the synthesis of the cementing substances of the capillary. The vitamin has been used with variable success in the treatment of ill-defined hemorrhagic syndromes due to increased vascular fragility (or permeability?), and to antagonize the bleeding due to Dicumarol overdosage. Favonoids of various types will (perhaps aspecifically) improve the bleeding tendency of that heterogeneous group called "vascular purpura" if given at high doses and over a long period of time. The endocrine system also plays a role in the control of the vascular mechanism of hemostasis. Ungar[12] has isolated from the spleen a substance ("splenin") which shortens the bleeding time, increases the vascular resistance and inhibits the release of histamine from injured cells. Liberation of "splenin" is mediated through the pituitary gland. Close in properties to splenin is "thrombocytosin"[13] a steroid, which, in addition to an effect on the number and function of circulating platelets, also improves the vascular resistance and is said to produce remission of bleeding in patients with idiopathic

FIGURE 5—SPECIFIC PLATELET CONSTITUENTS WITH BIOLOGICAL ACTIVITY

1. Vasoconstrictor Principle (Serotonin = 5 Hydroxytryptamine)
2. Clot Retracting Agent (?) = Retractoenzyme
*3. Platelet Thromboplastic Factor
   +Plasma Factors { Antihemophilic Globulin; PTC; PTA (?) } ⟶ Thromboplastin
4. Platelet Factor 1 (Affects conversion of prothrombin to thrombin)
5. Platelet Factor 2. (Affects conversion of fibrinogen to fibrin)
*6. Platelet Factor 3 (Antiheparin)
7. Antifibrinolysin (?)
8. Histamine
9. Hypotensive Principle

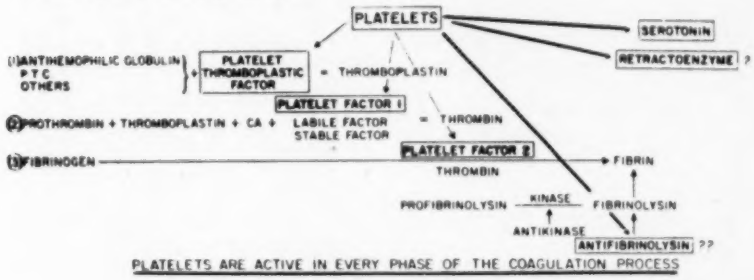
* Probably identical.

thrombocytopenic purpura even without elevation of the platelet count. Finally, ACTH and cortisone, while having only a variable effect on the platelet count and occasionally accelerating the clotting time, cause prompt and striking improvement of capillary resistance[14] and, rarely, a reduction of the bleeding time after prolonged administration. The mechanism of this effect is not clear but these hormones are used very successfully to control the clinical bleeding of patients with thrombocytopenia, megakaryocytic or amegakaryocytic (in addition to platelet transfusions), vascular pseudohemophilia and undefined "vascular purpura." The striking clinical response to ACTH of thrombocytopenic patients even in the absence of any effect on the platelet level, is in itself additional evidence of the great importance of the vascular factor in the control of hemostasis.

The Platelet Mechanism

Bizzozero[15] was perhaps the first investigator to realize fully the unique importance of platelets in the physiologic process of hemostasis and in the pathogenesis of thromboembolism. Recent studies have indeed emphasized the conclusion that platelets exercise a very complex and fundamental effect on the hemostatic process and the coagulation of blood in particular (Fig. 5). There is little doubt that the control of bleeding following injury to the vessels is greatly dependent on the function of platelets. As viscous bodies they mechanically plug the vessel wound. They cause vasoconstriction and initiate blood coagulation

FIGURE 6—THE FUNCTION OF PLATELETS IN THE HEMOSTATIC PROCESS (SCHEMATIC).

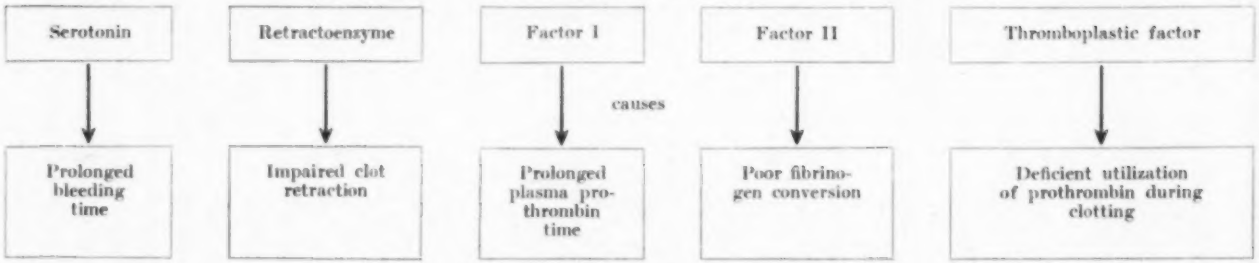


through the release of chemical agents at the time they agglutinate and disintegrate at the site of the vascular injury. It has been thus far believed that only intact, normally functioning platelets are able to determine clot retraction. More recently, however, Fonio[16] has suggested that clot retraction is due to a specific constituent of platelets (retractoenzyme), which has been isolated from the hyalomere of platelets. These results are stimulating, but need confirmation. Platelets are veritably small physiologic units, of extremely complex enzymatic and chemical structure. In addition to their function in the hemostatic process, platelets liberate a hypotensive principle and contain antifibrinolysin. As previously pointed out, platelets regulate practically all phases of the hemostatic process: (a) The generalized vasoconstriction which follows vascular injury is due, at least in part, to the release of serotonin; (b) disintegration of platelets releases the thromboplastic factor, which reacts with plasmatic agents to form thromboplastin, and factors 1 and 2 which accelerate conversion of prothrombin to thrombin and formation of fibrin respectively;[17] (c) platelets oppose the activity of heparin, probably by releasing another constituent (factor 3) which is probably identical with the platelet thromboplastic factor (Fig. 6).

The complex function of platelets is also demonstrated by the severity of the hemostatic defect in thrombocytopenic states. Thrombocytopenic patients show prolonged bleeding time and positive tourniquet test (increased vascular fragility), reduced utilization of prothrombin during clotting and increased sensitivity to heparin (deficiency of thromboplastic factor and/or factor 3); moderately delayed one-stage plasma prothrombin time (deficiency of factors 1 and 2), absence of clot retrac-

FIGURE 7—THROMBOCYTOASTHENIAS

Hemorrhagic diatheses due to deficiencies of one or more of the platelet factors



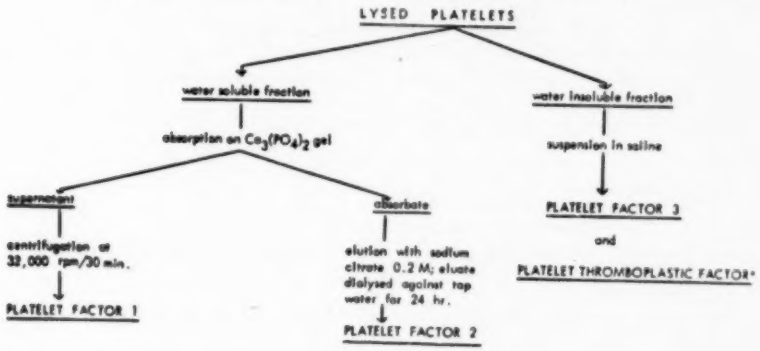
A GROUP OF RECENTLY STUDIED CASES

Name	*Age*	*Sex*	*Platelet count (x 10³/cu. mm.)*	*Bleeding time (Ivy) minutes*	*Prothrombin Activity Plasma %*	*Prothrombin Activity Serum %*	*Clot retraction %*
E.K.	16	M	567.0	*35*	95	*90*	31
R.D.	6	F	436.8	3	90	17	*2*
G.J.	47	F	549.1	6½	85	*92*	34
R.M.	4	F	501.0	*22*	80	15	39
E.K.	29	F	497.3	4	*30*	6	32

Selective, combined, total dysfunctions of platelet functions may occur. Common features included: (a) bleeding, common after injury or at surgery, spontaneous hemorrhage less common; (b) presence of large and bizarre platelets; (c) correction of the hemostatic defect by the transfusion of platelets.

Of the above group, the hemostatic defect of E.K. was one of the thromboplastic factor and of a hypothetical "vascular factor"; that of case R.D. was due to single deficiency of "retractoenzyme" (a hypothetical factor controlling the clot retraction); that of G.J. was due to single deficiency of platelet thromboplastic factor; that of R.M. was due to deficiency of "vascular factor" alone; that of E.K. to deficiency of platelet factors I and II.

FIGURE 8*—CRUDE SEPARATION OF THE PLATELET FACTORS TAKING PART IN THE PROCESS OF BLOOD COAGULATION



* No practical method of separation of the two water-insoluble factors is available at present. Figures 8, 9, 12 and 13 are from Stefanini, M.[22] in *Amer. J. Med. 14*:64-86, 1953. Reprinted by permission.

tion. The relationship of individual platelet factors to specific defects of the hemostatic mechanism, on the other hand, is illustrated by the findings in cases of thrombocytoasthenia.[18] In this hemorrhagic tendency, platelets are normal in number but they exhibit morphologic abnormalities (abnormal size, appearance and staining) and failure of one or more physiologic functions (Fig. 7). Clot retraction, utilization of prothrombin during clotting, slightly prolonged one-stage plasma prothrombin time, positive tourniquet test are present as isolated findings or in various combinations in these patients. In all, the hemostatic defect is corrected by the administration of viable platelets. Recently, platelets have become available in large amounts.[19,20] It has thus become possible to fractionate them and obtain individual chemical constituents in relatively purified form (Fig. 8). This approach has confirmed the existence of platelet factors with specific functions. As a result of these studies, some of the chemical constituents of platelets have been fairly well characterized by Van Creveld and Paulssen[21] and in our Laboratory (Fig. 9).[22]

However, while very detailed information has been obtained with regard to the physiologic structure and the function of platelets in hemostasis, we still lack very important and basic information. We cannot, at the present time, visualize clearly the mechanism which causes ag-

FIGURE 9—CHARACTERIZATION OF SOME OF THE PLATELET FACTORS

Platelet factor 1:*

(1) accelerates the conversion of prothrombin to thrombin
(2) water-soluble; precipitated from solution by 50% saturation with $(NH_4)_2SO_4$
(3) sediments following centrifugation at 32,000 r.p.m. for 30 min.
(4) heat labile (53°C.)
(5) non-absorbed on $Ca_3(PO_4)_2$ gel or $BaSO_4$

Platelet factor 2:

(1) accelerates the

$$\text{fibrinogen} \xrightarrow{\text{thrombin}} \text{fibrin reaction}$$

(2) water-soluble; does not precipitate from solution following centrifugation at 32,000 r.p.m. for 30 min.
(3) heat stable
(4) absorbed on $Ca_3(PO_4)_2$ gel and $BaSO_4$; can be eluted from them with sodium citrate

Platelet factor 3:†

(1) opposes the activity of heparin in the blood coagulation process
(2) water-insoluble, suspendable in saline solution
(3) relatively heat stable
(4) non-absorbed on $Ca_3(PO_4)_2$ gel or $BaSO_4$

Platelet thromboplastic factor:†

(1) interreacts with one or more plasma components to form active thromboplastin
(2) found mostly in platelets but also in other formed elements of the blood
(3) water-insoluble, partly soluble in citrate-phosphate buffer solution
(4) heat stable (relatively, at 56° C)
(5) precipitates following centrifugation at 32,000 r.p.m. for 30 min.
(6) high phospholipid content: similar in chemical structure to placental thromboplastin

* Many of the properties of this factor are shared by the "serum accelerator." The relationship of the two agents is a very close one.
† Platelet factor 3 and platelet thromboplastic factor are very similar in properties and are probably identical agents.

glutination of platelets at the site of vascular injury and we cannot explain why platelets are so unstable in contact with foreign surfaces. Equally little is known concerning the mechanism of platelet production from the megakaryocytes and of their delivery from the bone marrow into the peripheral circulation. We have only fragmentary knowledge of the factors which regulate the platelet level in the peripheral blood (possibly the same ones which regulate platelet production and delivery). Nutritional deficiencies (scurvy, pernicious anemia, etc.) cause reduced platelet formation; "hypersplenism" inhibits delivery and reduces the production of platelets by the megakaryocytes. The platelet level may be temporarily elevated by the administration of high doses of ACTH

FIGURE 10—WHERE THE VARIOUS COAGULATION FACTORS ARE FOUND

Platelets	*Plasma*	*Serum*
1. Platelet thromboplastic factor (platelet activator)	(a) *Agents favoring blood coagulation*	
	1. Antihemophilic globulin (AHG)	
2. Platelet factor 1	2. Plasma thromboplastin component (PTC)	1. PTC
3. Platelet factor 2	3. Plasma thromboplastic antecedent (PTA)	2. PTA (?)
4. Platelet factor 3 (anti-heparin factor)	4. Prothrombin	
	5. Calcium	
	6. Labile factor →	3. "Serum accelerator"
	7. Stable factor →	4. "Activated" (?) stable factor
	8. Fibrinogen	
	(b) *Agents opposing blood clotting or destroying the formed clot*	5. Thrombin 6. Metathrombin
	9. Antithromboplastins	(*)
	10. Antithrombins	
	11. Albumin X	
	12. Profibrinolysin	
	13. Antifibrinolysin	
	14. Antifibrinolysokinase	

* It also contains factors 9 to 14 of plasma, in relatively unmodified concentration.

FIGURE 11—CHARACTERISTICS AND PROPERTIES OF THE PLASMATIC

	Abbreviation	*Function in the Clotting Process*	*Its Deficiency Causes*	*Name of Clinical Bleeding Disease*	*Found in Cohn's Fract.*	*Precipitated from Plasma by:*	*Fate During Clotting of Blood*
Anti-hemophilic Globulin	AHG	+ Platelets, PTC, (?) PTA Forms Thromboplastin	Deficient Utilization of Prothrombin During Clotting	Hemophilia	I	(a) Saturation with CO_2 of Diluted Plasma (b) 33% Saturation with $(NH_4)_2SO_4$	Quickly and Almost Completely Utilized
Plasma Thromboplastic Component	PTC	+ Platelets, AHG, (?) PTA Forms Thromboplastin	—Ditto—	PTC Deficiency	IV	40-50% Saturation with $(NH_4)_2SO_4$	Almost Completely *non* Utilized
Plasma Thromboplastin	PT	+ Calcium, Labile and Stable Factor Converts Prothrombin to Thrombin	—Ditto—			25% Saturation with $(NH_4)_2SO_4$	Utilized in Great Part
Prothrombin		+ Calcium, Labile and Stable Factor, Thromboplastin Produces Thrombin	Poor Formation of Thrombin	True Hypoprothrombinemia	III-2		75-85% Utilized for Formation of Thrombin
Stable Factor	SF	+ Calcium, Labile Factor, Thromboplastin, Prothrombin Produces Thrombin	Poor and Slow Formation of Thrombin	False Hypo-Prothrombinemia (Convertin Deficiency)	III-2		Very Little Utilized
Labile Factor	LF	+ Calcium, Stable Factor, Thromboplastin, and Prothrombin Produces Thrombin	—Ditto—	False Hypoprothrombinemia (Parahemophilia)	III	(a) 10% Cold Ether, pH 5.4 from Dil. Pl. (b) 45% Saturation with $(NH_4)_2SO_4$	Utilized and Activated to Serum Accelerator
Fibrinogen		Converted to Fibrin by Thrombin	No or Poor Blood Clot	Hypo- and Afibrinogenemias	I-2	(a) Weak Acids (b) 8% Cold Ethanol (c) 50% Saturation with NaCl; 25% Saturation with $(NH_4)_2SO_4$	Completely Converted to Fibrin
Thrombin		Converts Fibrinogen to Fibrin			Albumin	Acidification to pH 5.1 in the Cold	See: Mechanisms of Thrombin Inactivation
Profibrinolysin		Lysis of Clot after Activation only	Activation causes excessive blood destruction. Deficiency may cause thrombotic tendency	Purpura Fibrinolytica	III-3	(a) 33% Saturation with $(NH_4)_2SO_4$ (b) Acidification to pH 5.3	?

FACTORS OF BLOOD COAGULATION AND THEIR DERIVATIVES

Fate During Storage of Plasma	*Heat Stability*	*Solubility*	*pH Range of Activity*	*Effect of Dicumerol on Conc.*	*Absorption on Gels and Filters*	*Remarks*
50% Destroyed in 12 Hours, Stable in Frozen, Lyophilized Pl.	Stable at 56°C	Water Soluble		None	None	
Stable	Stable at 56°C for 30′		4-11.2	None	Absorbed from Oxalated Plasma, Can be Eluted with Sodium Citrate	
Relatively Stable (50% Loss in 1 Week)	—Ditto—	Water Soluble	Wide	None	Absorbed from Citrated Plasma, Can be Eluted with Saline	
Stable	Relatively Labile (40-60°C)	Water Soluble	Isoelectric Point 4.2	Concentration Reduced	Absorbed from Oxalated Plasma, Can be Eluted with Sodium Citrate	α_1-Globulin, S-containing Glycoprotein
Very Stable	56°C for 30′		4-8	—Ditto—	—Ditto—	Retained on 30% Asbestos Filter (Cow Plasma)
Very Labile (More Stable in Citrated Plasma)	Destroyed at 56°C	Water Soluble	4-10.5	None	None	Restores Clotting Defect of Aged Plasma
Fairly Stable	Clots Irreversibly at 56°C	Soluble in Saline Solution	Isoelectric Point 5.3	None	None	*Fibrin* Has Essentially Similar Properties
	Relatively Labile (40-60°C)	Water Soluble		Indirectly Decreased Concentration	None	Contains S and Carbohydrates
	Relatively Labile	Water Soluble	4.5-8	None	None	

and cortisone and, at times, by the administration of extracts of the thymus gland,[23] of polycythemic blood[24] and blood from recently bled donors. These may all contain megakaryocyte-stimulating factors. Transfusion of normal plasma, on the other hand, causes in many cases temporary reduction in the platelet count, due to the activity of a thrombocytopenic globulin.[25] Even without commenting on changes in viscosity, adhesiveness and fragility of platelets, which have been repeatedly discussed in relation to "blood hypercoagulability" and thromboembolic tendency, it is easy to see that many questions remain unanswered with reference to the role of platelets in hemostasis.

The Blood Coagulation Mechanism

In addition to those supplied by the platelets, a number of plasma factors take part in the process of blood coagulation (Fig. 10). They can be divided into three groups: (a) those needed for the formation of thromboplastin: antihemophilic globulin (AHG), plasma thromboplastic component (PTC), ? plasma thromboplastic antecedent (PTA); (b) those entering into the formation of thrombin: prothrombin, calcium, labile factor, stable factor; and (c) fibrinogen. The characteristics and properties of the various agents are presented in Figure 11. Several denominations have been recommended for many of these factors. Synonyms for the various clotting agents are presented in Figure 12. There are, in addition, agents which oppose the formation of the fibrin clot: natural antithromboplastin and antithrombins, albumin X; and factors which are part of the fibrinolytic mechanism: profibrinolysin, antifibrinolysokinase, antifibrinolysin.

The fate of these factors during the clotting process is very significant in understanding their role in blood coagulation. Many are utilized in part or completely, others are not and are found in unchanged concentration or activity in the serum. The first group probably enters in quantitative interactions during the coagulation of blood; those of the second group most likely act as catalysts of the reaction. Fibrinogen is completely utilized; very little AHG and prothrombin are left in the serum after completion of clotting. Labile factor is almost completely utilized, being converted to the more active agent, the serum accelerator. This agent, in turn, disappears quickly after completion of coagulation. PTC and stable component, and calcium are little or not at all utilized during clotting and their concentration is practically unchanged.

FIGURE 12—SYNONYMS OF VARIOUS FACTORS IN THE COAGULATION OF HUMAN BLOOD(*)

1. *Factors taking part in the activation of thromboplastin:*

PLATELET THROMBOPLASTIC FACTOR
- thromboplastinogenase
- platelet activator
- cellular thromboplastic component (TCC)†

PLASMA THROMBOPLASTIC FACTOR
- prothrombokinase
- plasmakinin
- antihemophilic globulin
- thromboplastinogen
- thrombocytolysin
- thrombokatalysin
- thromboplastic plasma component (TPC)†

2. *Tissue thromboplastin*
- thrombokinase
- cytozime
- thromboplastic protein
- thrombokinin

† Not to be confused with PTC (plasma thromboplastic component) (see text)

3. *Factors involved in the conversion of prothrombin to thrombin* (other than calcium and thromboplastin)

"LABILE FACTOR"
- thrombogène
- component A of prothrombin
- factor V → factor VI
- accelerator factor
- co-factor of thromboplastin
- plasma Ac-globulin → serum Ac-globulin
- proprothrombinase → prothrombinase
- prothrombinogenase → thrombinogenase
- ? prothrombinokinase → thrombokinase(**)
- plasma prothrombin conversion factor (PPCF) → serum accelerator
- proaccelerin → accelerin

"STABLE FACTOR"
- co-factor V
- ? component B of prothrombin
- prothrombin accelerator
- prothrombin conversion factor
- prothrombin converting factor
- co-thromboplastin
- plasma precursor → serum prothrombin conversion accelerator (SPCA)
- proconvertin → convertin
- factor VII
- ? prothrombinogen (inactive prothrombin)
- kappa factor (in chicken)

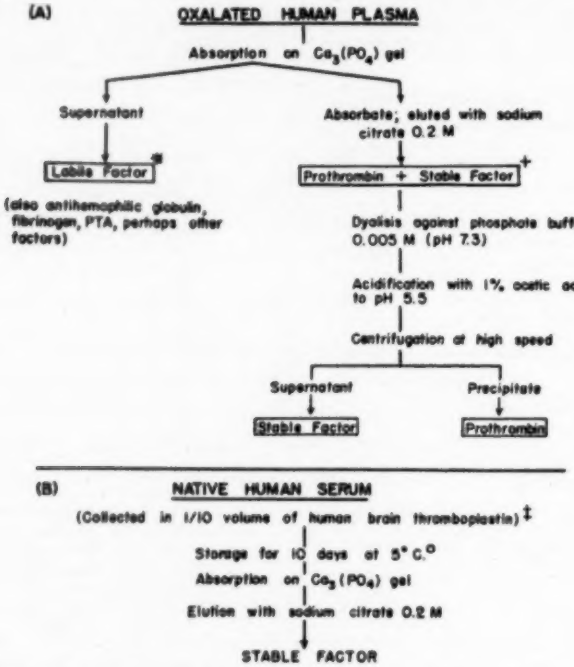
(**) In the meaning of an agent capable of influencing the conversion of prothrombin to thrombin

* Many of the factors in group 3 are very likely: (a) mixtures of "labile factor" and "stable factor"; (b) even more probably, mixtures of "stable factor" and "prothrombin"; (c) possibly, intermediate steps in the prothrombin → thrombin conversion and thus prothrombin derivatives.

Some of the factors are arranged in couples, joined by an arrow. Those at the right of the arrow are considered less active precursors found in plasma; those to the left of the arrow, the active (or more active) form found in the serum. For this reason, some investigators prefer to think of "labile factor" and "stable factor" in terms of a system and not as an isolated agent.

Characterization of most of the known coagulation factors has now proceeded to a point where their existence can no longer be doubted. Perhaps some doubt remains with regard to the relationship of prothrombin to the stable factor, since the physical and chemical characteristics of the two agents are practically identical. Prothrombin and stable factor can be separated, at considerable loss of activity of both agents, by

FIGURE 13—CRUDE SEPARATION OF THE PLASMA FACTORS TAKING PART IN THE CONVERSION OF PROTHROMBIN TO THROMBIN.



* The "labile factor" can be specifically precipitated by acidifying the diluted plasma to pH 5.4.
\+ In bovine plasma prothrombin and "stable factor" can be separated easily (although with large loss of both factors) by filtering the plasma through 30% asbestos filters. The "stable factor" is retained on the filter, prothrombin passes through. The "stable factor" can then be eluted with sodium citrate from the filter pad.
‡ To cause complete utilization of prothrombin, thus eliminating this agent from the serum.
° To destroy or inactivate the "labile factor" not utilized during the process of blood coagulation and the "serum accelerator" developed during the clotting of blood.

absorption on asbestos filters (cow plasma),[26] by chromatographic techniques (human plasma),[27] and by chemical separation.[28] But the possibility remains that stable factor might represent either a less active precursor[29] or a derivative of prothrombin. Many of the factors can be obtained from plasma in a highly purified state, but only at the cost of great loss of all others. Figure 13 illustrates the separation of prothrombin from stable and labile factor. Final products from plasma and serum are of relative purity only.

The study of the interaction of the various individual factors represents the most difficult part in the study of the blood coagulation mechan-

FIGURE 14

THEORIES OF THE MECHANISM OF BLOOD COAGULATION

ism. The theories of various investigators in the field have been reviewed recently [22] and they will not be discussed here. On the basis of careful analytical study and of the results of tests indicating with sufficient accuracy the nature of the hemostatic defect in the bleeding patient, it is now generally felt that the process of blood coagulation can be divided into at least three phases (Fig. 14). Many others must certainly exist and are being gradually recognized. The first phase is the *formation of thromboplastin.* The bleeding diseases of this group (hypothromboplastinemias) have in common a deficient utilization of prothrombin during clotting and include the hemophilia syndrome and the thrombocytopenic states. At least three and possibly four factors take part in the reaction: platelet activator or thromboplastic factor, AHG, PTC and, possibly, PTA. This phase of the clotting process has probably received the greatest amount of attention in the past year. After the discovery by Quick[30] and by Brinkhous[31] that the interaction of platelet and plasmatic factors was needed to form thromboplastin, one advance quickly

followed another. Hemophilia was recognized to be a disease of defective formation of thromboplastin. The exhaustive study of this disease, however, and particularly of the clotting ability of hemophilic blood and of the therapeutic response of hemophiliacs to various agents revealed a number of paradoxes: 1) the ability of some hemophilic-plasmas to correct each other's defect; 2) the possibility of obtaining normal yield of AHG from plasma of some hemophiliacs; 3) the lack of response of some hemophilic patients to the administration of purified AHG; 4) the favorable response to *stored* plasma of some cases of hemophilia, but not of others (requiring, on the contrary, *fresh* blood). The interpretation of these observations on which, I am sure, Dr. Brinkhous will comment more fully later, has come from the work of three main groups of investigators: Schulman and Smith,[32] Aggeler and co-workers,[33] and Biggs and co-workers[34] in England. It has led to the discovery of PTC. A further extension of this work has come from Rosenthal and co-workers[35] which has suggested that another factor (PTA) may take part in the formation of thromboplastin. PTC is strikingly different from AHG and, if not a derivative of the platelet-AHG interaction, should represent a new clotting agent. More doubt has been expressed with regard to PTA. The deficiency of this factor has been suggested by some[36] to represent a combined deficiency of PTC and AHG. The properties of PTA are, indeed, intermediate between those of PTC and AHG. If this is true, it would avoid the postulation of a new clotting agent to explain the results of Rosenthal et al.[35] A more complete study of this agent would certainly be welcome and, I am sure, is under way by its discoverers.

The nature of the reaction among the three and, possibly, four factors is not completely clear. AHG and platelet thromboplastic factor interact according to definite quantitative proportions[37] and are both utilized almost completely during the coagulation of blood. The role of PTC, however, is not clear as yet, since the factor is found in practically unmodified concentration in the serum and may act only as a catalyst of the AHG-platelet reaction. In any case, studies by MacFarlane and co-workers ("thrombin generation test"), by Biggs and co-workers ("thromboplastin generation test"), have done much to prove that deficiency of AHG (hemophilia), PTC (PTC deficiency) and PTA (PTA deficiency) belong together in the group of diseases where the activation of thromboplastin is limited and slow. We have reached the same con-

clusion by the study of the concentration of plasma thromboplastin in these patients. Dr. Campbell, now of Portland, Ore., and I have been able to isolate from citrated plasma a thromboplastic agent which develops when platelet-rich human plasma is incubated in glass. A method for the direct determination of the activity of plasma thromboplastin[38] has been developed showing that this intermediary factor is only slowly and incompletely formed in patients with hemophilia, PTC or PTA deficiency, and thrombocytopenia and thrombocytoasthenia of some type. It may be added that the successful isolation of plasma thromboplastin is one of the first attempts to separate from human plasma products which represent not primary factors, but rather intermediary phases of the blood coagulation mechanism.

The nature of the second phase of the coagulation process, the *conversion of prothrombin to thrombin*, is the source of bitter controversy. Abnormalities of this phase include the hypoprothrombinemias, characterized by a delayed one-stage prothrombin time of plasma. Thromboplastin (formed during the first phase of the coagulation process), calcium, two accessory factors (labile and stable) are necessary to convert prothrombin to thrombin. By some investigators this conversion is interpreted as a stoichiometric process. Others, however, consider thromboplastin, calcium, labile and stable factors as mere accelerators of the conversion of prothrombin to thrombin. Facts, often obtained with a completely different experimental approach, can be quoted in support of one or the other point of view. Thus (a) thrombin does not contain thromboplastic material or ionic calcium (but may contain bound calcium); (b) the molecular weight of thrombin is smaller than that of prothrombin; (c) thrombin evolves slowly but spontaneously in a solution of purified prothrombin in 25 per cent sodium citrate;[39] (d) the stable factor is apparently not utilized during the process of blood coagulation.[40] If one accepts these results, one must conclude that prothrombin contains all materials necessary for the formation of thrombin and that calcium, thromboplastin, stable and labile factors can affect only the rate of the conversion of prothrombin. On the other hand: 1) concentration of available thromboplastin and of calcium is the limiting factor in the amount of prothrombin which can be converted to thrombin; 2) labile factor is utilized quantitatively in the formation of thrombin, serum accelerator evolving at the same time;[41,42] 3) no thrombin can apparently evolve in a mixture of prothrombin, thromboplastin and

calcium in the absence of labile factor.[43] The same holds true, in our experience, in the case of the stable factor. These findings would then suggest that prothrombin, calcium, thromboplastin and, at least, labile factor interact according to definite quantitative proportions, and that the reaction may be stoichiometric in nature. All these experiments, which are perhaps too hastily translated into established facts, are, however, not above criticism. To comment only about two of them, on which depends heavily the thinking of the opposing groups of investigators, one would have reason to dispute the "purity" of many of the isolated coagulation factors used in these experiments. Despite remarkable efforts on the part of many, absolutely pure coagulation factors are not available as yet. On the other hand, decrease in concentration or activity of any coagulation factor during the formation of thrombin is not definite evidence of a stoichiometric reaction, especially when it is known that, while some of these factors decrease, more active ones develop.

There are other findings further confusing the kinetics of the second phase of the coagulation process. Evidence that calcium may act in the coagulation of blood only when bound to proteins has been reviewed and strengthened.[44] The relationship of prothrombin to thrombin remains partially unsolved. The two agents present certain affinities of chemical composition, but the molecular weight of thrombin is smaller than that of prothrombin. Recently Lorand et al.[45] have studied the mechanism of formation of thrombin from prothrombin in 25 per cent sodium citrate solution. Thrombin formation, in their experiments, proceeded in two steps. Carbohydrate and nitrogen were released first from the prothrombin molecule; thrombin was then formed autocatalytically from the intermediate derivative of prothrombin. These experiments support the hypothesis that thrombin is a product of "degradation" of prothrombin, but do not help greatly in understanding the role of the "accessory" factors (thromboplastin, calcium, labile and stable factors) in the formation of thrombin besides implying that they are mere accelerators.

Flynn and Coon[46] have recently presented a veritable contribution to the understanding of the second phase of the coagulation mechanism. It has been thought for some time that several reactions take place during the conversion of prothrombin to thrombin, some of them involving preliminary interaction of thromboplastin, labile and stable factors, and calcium to form intermediate complexes. Thus, Owren[26] has postulated

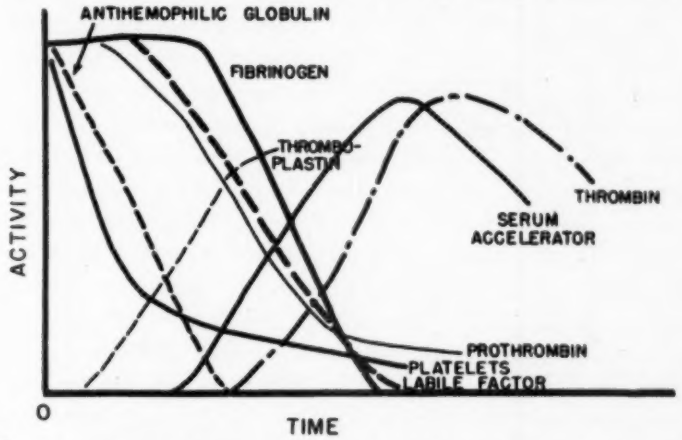
that, in an early phase of the process of thrombin formation, thromboplastin and calcium react with proconvertin to form convertin. Flynn and Coon have demonstrated by direct techniques of isolation that thromboplastin and labile factor, thromboplastin, calcium and stable factor are able to form intermediate complexes, none of which, however, can convert prothrombin to thrombin. The mixture of thromboplastin, calcium, labile factor and stable factor, however, forms a complex (quickly settling in the centrifuge), which easily converts prothrombin to thrombin. These observations not only reemphasize the step-like nature of the second phase of the coagulation mechanism, they also support the contention that many of the accelerators of the conversion of prothrombin to thrombin described in the literature may, in effect, be intermediary complexes of two or more of the factors taking part in the reaction. It may probably be concluded on the basis of the available evidence that the kinetics of the conversion of prothrombin to thrombin are still perhaps a mysterious, but certainly a controversial question. If, however, we shift our interest to the bleeding patient, it becomes obvious that marked deficiency of any of the factors known to take part in the formation of thrombin, whether indispensable or not by in vitro studies, is accompanied by severe bleeding manifestations, an indication that the hemostatic mechanism has become grossly inadequate. From the clinician's point of view, effective protection against hemorrhage requires the presence in concentrations above the critical level of *all* factors known to play a role in the coagulation of blood.

The third phase of the clotting process consists in the *gelification of fibrinogen to fibrin*. A few authors believe that the reaction is proteolytic in nature. Laki[47] thinks that thrombin makes fibrin molecules from fibrinogen by splitting off peptides (these peptides contain approximately 3 per cent of the original N and are composed of at least twelve amino acids, including aspartic and glutamic acid). Lorand and Middlebrook[48] state that fibrinogen is converted to fibrin by losing two α-amino groups of glycine through the action of thrombin. These results, obtained with bovine fibrinogen, are probably not applicable to human physiology in their entirety. Still another point of view has been postulated, with Lyons[49] as its most vigorous proponent. It is believed that thrombin is able to oxidize the sulfhydril (SH-HS to S-S) group of fibrinogen. According to Lyons, the fibrinogen → fibrin reaction would occur in two steps: first, the S-H groups of fibrinogen would be freed;

secondly, the S-H groups would be oxidized, probably by the activity of the naphthoquinone groups present in the thrombin molecule. Fibrinogen B has been identified by Lyons as an intermediary product of the fibrinogen → fibrin conversion. Curiously enough, according to Lyons, fibrinogen B can be easily precipitated from plasma by the addition of β-naphtol in patients with thromboembolism or thrombotic tendency. Due to the obvious diagnostic importance of such findings, we and others have tried to confirm Lyons' results, but without success. The prevailing view today is that human fibrinogen and fibrin are essentially identical and exhibit identical antigenic properties. They yield identical degradation products on enzymatic digestion. The nature of the fibrinogen → fibrin reaction seems to consist of a molecular rearrangement. It appears that, after a preliminary end-to-end arrangement, the long molecules of fibrinogen undergo a process of tri-dimensional polymerization.[50, 51] Thus fibrin comes into being, the fibrinogen molecules not losing their individuality. The significance of other coagulation factors in the fibrinogen → fibrin reaction is not clearly defined. It is known that platelet extracts (platelet factor 2) accelerate the conversion of fibrinogen and that calcium may play an important role in the primary process of polymerization of the fibrinogen molecules.[51] The fate of thrombin itself is not very clear. It is possible that it might unite temporarily with fibrinogen while this is converted to fibrin. This fibrinogen-thrombin reversible combination may represent the less soluble, less stable and already partially denatured fibrinogen derivative (different from fibrinogen B), defined by Apitz as *profibrin*. Thus, even in this apparently clear-cut phase of the blood coagulation mechanism, a number of important questions remain unanswered.

At the end of this analytical and necessarily concise presentation of the various phases of the clotting mechanism as we visualize it in the test tube, it is perhaps useful to try to visualize the sequence of events as they might occur dynamically "in vivo" (Fig. 15). Platelet agglutination and lysis are the first step of the process. As platelet products become free, AHG is utilized (the role of PTC and PTA remaining to be better explored) and thromboplastin develops. Thromboplastin, calcium, labile and stable factors then form probably several intermediary complexes and prothrombin is converted to thrombin. As thrombin is formed, labile and, perhaps, stable factors are activated, thrombin formation is greatly accelerated and the fibrin clot appears. Such concept

FIGURE 15—DIAGRAMMATIC REPRESENTATION OF THE SEQUENCE OF EVENTS AND OF THE FATE OF VARIOUS CLOTTING FACTORS DURING THE PROCESS OF COAGULATION OF NATIVE PLASMA.*



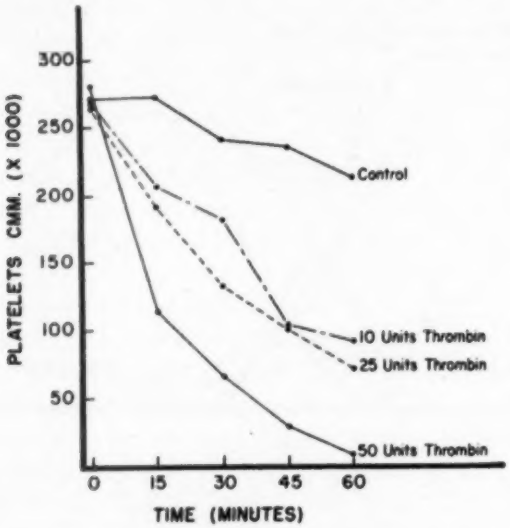
* Platelets are agglutinated and presumably lysed and, at the same time, antihemophilic globulin activity decreases rapidly and thromboplastin appears in the plasma. Then, as the activity of prothrombin and labile factor decreases rapidly, serum accelerator and thrombin are found in increasing concentration. As the activity of thrombin increases, fibrinogen is converted to fibrin. At a later time, but within few minutes of the completion of clotting, the activity of thrombin and serum accelerator decreases rapidly. PTC, stable factor and calcium are not included, since they do not seem to undergo any significant change of activity during clotting. Most of these data were obtained from the study of a patient with severe acquired (but selective) hypofibrinogenemia and agree fairly well with those described by Alexander et al. in cases of congenital afibrinogenemia. (Abstract, *Fed. Proc. 12*:167, 1953).

is, of course, highly hypothetical, but does not disagree radically with any of the observations in the test tube and those obtained in living animals by methods which visualize the circulation of blood in the capillary bed and the changes following hemorrhage.

The Autocatalytic Mechanisms

The final consideration of the preceding section leads us to discuss other basic mechanisms of hemostasis, those of autocatalysis. In man, the hemostatic process cannot be fully effective in the control of bleeding, unless a solidly anchored fibrin clot can be formed. This, in turn, requires sufficient accumulation of thrombin at the site of vascular injury, accumulation which is limited by the washing effect of blood pouring from the wound, while the enzyme is also neutralized by various inhibitory agents. The autocatalytic mechanism assures that enough thrombin and other important clotting factors are available at the site

FIGURE 16—EFFECT OF PURIFIED HUMAN THROMBIN ON THE COUNT OF SUSPENSIONS OF PLATELETS IN DEPROTHROMBINIZED SERUM.



From Stefanini, M.,[52] in *Acta med. scand. 140*:290-306, 1951. Reprinted by permission.

of injury. In a previous article we have discussed the development of the all-important concept that blood clotting, once initiated, proceeds at ever increasing speed and presented experimental evidence for it.[52] Experiments of many authors since Arthus seem to indicate that thrombin itself, the end product of the "preparatory" or "latent" phase of the coagulation process is, in effect, responsible for the autocatalytic phase of the clotting process. It is possible, although not established, that other factors in plasma or serum may be necessary for the initiation of the autocatalytic reaction by thrombin.

The autocatalytic mechanism involves two basic reactions, both apparently set in motion when a small amount of thrombin is formed: (a) agglutination and lysis of platelets; (b) conversion of the "labile factor" to "serum accelerator." It is possible that thrombin may also (c) convert stable factor into a more active agent, as postulated by Alexander[53] and Owren[26] but denied by others and, as Quick et al.[54] have recently postulated, (d) activate AHG prior to its reaction with platelets.

What is the available evidence that platelets and thrombin are involved in one of the autocatalytic mechanisms? It is known that no autocatalytic reaction takes place when no platelets are available and when no thrombin can be formed (as in decalcified plasma). This is, of course, extremely indirect evidence. A perhaps more direct approach is that of DesForges and Bigelow[55] who have demonstrated that the conversion of prothrombin in platelet-poor plasma is greater when thrombin-treated platelets rather than untreated platelets are added. Evidence of a more direct nature is also available. Thus, when purified human thrombin is added to a suspension of platelets in serum (even if this is deprothrombinized) platelets agglutinate and are lysed (Fig. 16). Recently, de Robertis et al.[56] have observed by electron microscope changes occurring in platelets after treatment with thrombin. As shown in Figure 17, platelets, even when washed free of plasma or serum, are lysed and disintegrated by purified thrombin.

The second autocatalytic mechanism involves the conversion of the labile factor to serum accelerator. Ware and Seegers[57] first showed that, in the test tube, purified thrombin will activate plasma to serum Ac-globulin. These two factors are very likely identical with labile factor and serum accelerator respectively. We and others were able to demonstrate two significant facts: (a) There is a direct quantitative relationship between amount of prothrombin utilized during clotting (and thus, presumably, of thrombin produced), labile factor activity lost and activity of serum accelerator developed during the coagulation of blood; (b) serum accelerator activity develops if deprothrombinized plasma (which has lost prothrombin and stable factor but retains the greatest amount of labile factor) is treated with thrombin. Since we know that serum accelerator is a better accelerator of the formation of thrombin than labile factor, the development of serum accelerator results ultimately in greater and faster formation of thrombin. This step may be considered the dividing line between the "slow", "latent" phase and the accelerated "autocatalytic" phase of the coagulation of blood.

The significance of the autocatalytic mechanisms of blood coagulation may deserve comment. We have mentioned already that anticoagulants and the washing effect of bleeding neutralize and wash away, respectively, thrombin and prevent its accumulation in amounts sufficient to form a firm fibrin clot. More subtle reasons can also be offered why it can be expected that, without a mechanism of autocatalysis, the

FIGURE 17

THE AUTO-CATALYTIC MECHANISM OF BLOOD COAGULATION

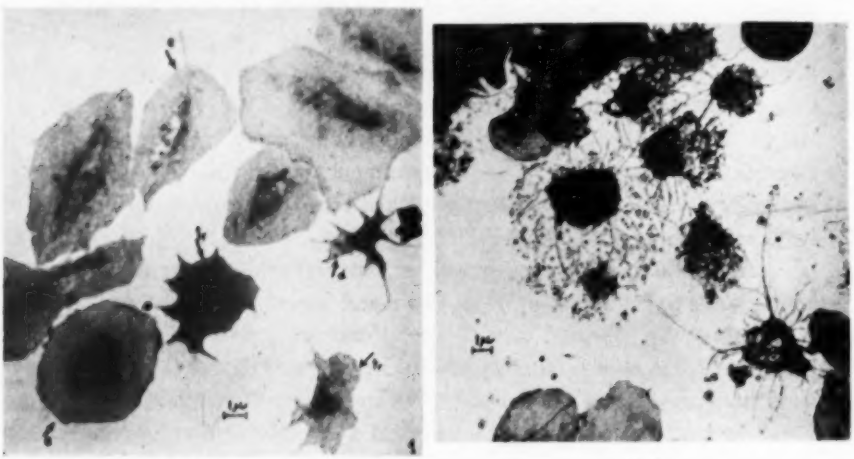
Thrombin may represent the key substance in this mechanism:

(1) It produces agglutination and lysis of platelets (possibly in the presence of a plasmatic factor) and, thus, the release of more platelet thromboplastic factor and platelet factors 1 and 2.

(2) It converts "labile factor" into "serum accelerator," thus greatly increasing the yield of thrombin and the speed of formation of this enzyme.

(3) It *may* also convert the "stable factor" into a more active derivative which is said to be present in serum.

THE EFFECT OF THROMBIN ON PLATELETS



17 a 17 b

THE AUTO-CATALYTIC MECHANISM REPRESENTS, HOWEVER, A POTENTIAL DANGER TO THE INDIVIDUAL

From DeRobertis, et al.[58] in *Blood* 8:587-97, 1953. Reprinted by permission of the authors and the publisher, Grune & Stratton, Inc.

formation of thrombin might be insufficient for hemostatic needs.[58] Without autocatalysis, any chemical reaction, stoichiometric or catalytic in nature, slows down after a period of maximum activity. Thus, the production of thrombin would tend to decrease as the process of blood coagulation continues. Also, the presence of an active autocatalytic agent (thrombin) on the surface of the clot guarantees that this will grow in size (as successive layers of fibrin are deposited) and will be anchored firmly. Finally, the continuous lysis of platelets maintains a steady supply of serotonin and this, in turn, assures steady vasoconstriction, necessary for a normal hemostatic mechanism.

The autocatalytic reaction may also help to explain why the defi-

FIGURE 18—PHYSIOLOGIC ANTICOAGULANTS

1. *All plasma proteins* (particularly globulins), capable of absorbing coagulation factors on their surfaces, thus decreasing their available concentration.
2. *Antithromboplastin*
*3. *Anti-accelerin* (?)
*4. *Anti-convertin* (?)
5. *Natural antithrombin*
6. *Heparin co-factor* (Albumin X)
7. *Fibrin clot*
8. POTENTIALLY: the fibrinolytic system (fibrinolysin and fibrinolysokinase), capable of destroying the formed fibrin clot.

* May represent an aspecific protein absorption effect.

ciency of single coagulation factors must be of severe degree before bleeding occurs. We see every day that the hemostatic mechanism is grossly normal and no bleeding occurs in patients with plasma prothrombin activity as low as 20 per cent, with labile factor activity as low as 25 per cent of normal, with platelet level of 60,000-70,000/c. mm. or less. The autocatalytic mechanisms possibly allow full utilization of the relatively deficient factors, and, thus, on it greatly depends the sufficiency of the hemostatic process in man.

ANTICOAGULANT MECHANISMS

The process of autocatalysis, while so important in maintaining efficient hemostasis and affording protection against hemorrhage, has in itself the impending danger of continued intravascular coagulation, until the damage caused to the organism through vascular occlusion might be greater than the benefit due to the prompt control of hemorrhage. Such ultimate possible effect of an otherwise extremely useful mechanism emphasizes the delicate balance upon which the hemostatic process is based.

The danger of extensive autocatalytic intravascular coagulation is checked and controlled by the availability of anticoagulant mechanisms (Fig. 18), some well defined, others which remain to be fully evaluated. *Absorption of active clotting agents on plasma proteins* (particularly globulins) as well as on fibrin may represent an aspecific but effective reaction. As clotting factors are absorbed onto the surface by proteins, their concentration is reduced and the clotting mechanism inhibited. It

is quite possible that hypothetical inhibitory agents against labile and stable factors (such as postulated by Owren) may be the expression of an absorption effect by plasma proteins. While this concept is mostly speculative, the antithrombin role of the *fibrin clot* has been well established by the studies of Foà[59] and Wilson.[60] The fibrin clot, large and spongious, is capable of absorbing thrombin on its surface, when this enzyme is produced at accelerated rate through the autocatalytic reaction. Fibrin clot removes formed thrombin from the site of injury thus decreasing the rate of the autocatalytic reaction, which depends on the concentration of available thrombin. The enzyme is, of course, slowly released later as the fibrin clot retracts, to be disposed of by the antithrombin mechanisms.

Very interesting from a theoretical standpoint is the presence of direct inhibitors of the first and second phase of the coagulation process (antithrombins and antithromboplastins) in the circulating blood. There is some evidence that at least two different *antithromboplastins* may be found in human plasma and serum. One, an inhibitor of *tissue* thromboplastin, is a water-soluble, heat labile factor requiring calcium for its activity.[61] The other, an inhibitor of *plasma* thromboplastin, is a lipoid substance extractable with ether or destroyed by it. It cannot be detected easily in normal plasma or serum, but it may be increased in rare bleeding conditions and, according to Tocantins, the hemostatic defect of hemophilia is, at least in part, due to its presence in excess. These two "physiologic" antithromboplastins should not be confused with another which may develop as the result of a process of iso-immunization in patients with hemophilia receiving multiple transfusions, in pregnant women with Rh-incompatible child, in pemphigus, lupus erythematosus, etc. This anticoagulant rarely inhibits thromboplastin directly,[62] most often inhibits the interaction of platelet and plasma factors to form thromboplastin.[63] Neutralization or inactivation of thrombin is the result of several mechanisms (Fig. 19). The thrombin-neutralizing role of the fibrin clot has been described already. Heparin, traces of which are apparently present in normal blood, is also able to neutralize thrombin if a plasmatic factor (albumin X) is also available. The most important thrombin neutralization mechanism, however, is probably represented by a heterogeneous group of factors found in the albumin fraction of plasma and serum and designated collectively as *antithrombin*. Thrombin is apparently absorbed onto the surface of antithrombin and this com-

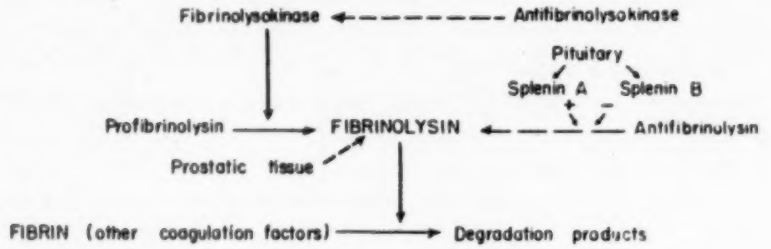
FIGURE 19—MECHANICS OF NEUTRALIZATION AND INACTIVATION OF THROMBIN

1. Interference of heparin and heparin co-factor (albumin X) with the action of thrombin on fibrinogen.
2. Neutralization of thrombin by natural antithrombin (the two agents form a reversible combination designated as METATHROMBIN).
3. Absorption of the thrombin on the fibrin clot.
4. Destruction of thrombin by a serum factor (?)

bination (which is reversible) is known as *metathrombin*. More recently, Seegers and associates[64] have postulated an additional antithrombin mechanism. At least in the dog, during and shortly after the coagulation and the activation of prothrombin, a substance develops in plasma from which antithrombin has been removed, capable of destroying thrombin activity. This substance apparently is one of the factors entering in the formation of thrombin.

In pathologic conditions, another antithrombic mechanism (in the broad sense of the term) can be found. Extremely rare cases of hemorrhagic tendency on the basis of deficient fibrin formation may be due to excess of individual plasma protein fractions. This occurs in "macroglobulinemia"[65] where hemorrhagic tendency is associated to an excess of "20s" ultracentrifugation plasma protein component, and, very occasionally, in cases of multiple myeloma when no significant thrombocytopenia is found but there is a striking increase of some of the globulin fractions. In both cases, the fibrinogen conversion by thrombin, perhaps the formation of thromboplastin are inhibited by the pathologic protein. The dilution of plasma in vitro and the replacement of abnormal with normal plasma in vivo correct the coagulation defect promptly but temporarily. High globulin concentration may also contribute to the bleeding tendency of liver dysfunction. As mentioned in the introductory remarks, these patients often present a very inclusive abnormality of the hemostatic mechanism. They occasionally have thrombocytopenia, very often reduction of activity and concentration of AHG, prothrombin, labile factor, stable factor, fibrinogen (due to liver insufficient synthesis of these various proteins). They also occasionally exhibit increased antithrombin activity, increased fibrinolytic activity and decreased vascular resistance (positive tourniquet test). In our experience, however, bleeding of patients with liver dysfunction is particularly im-

FIGURE 20—THE FIBRINOLYTIC SYSTEM IN HUMAN BLOOD.



Profibrinolysin (plasminogen, tryptogen, prolysin, lytic factor, etc.) found in plasma and serum is activated to *fibrinolysin* (plasmin, tryptase, tissue lysin, etc.) by a *fibrinolysokinase* (found in tissues, especially lung and uterus). The action of the kinase is probably inhibited or antagonized by inhibitors present in plasma and serum (*antifibrinolysokinases*). The active fibrinolysin is antagonized and inhibited by *antifibrinolysin* (antiplasmin), also found in plasma and serum. Alternatively, a proteolytic enzyme (similar to, but not identical with fibrinolysin) of prostatic origin may also lyse fibrin clots (disseminated prostatic carcinoma). Moreover, other proteolytic enzymes may also be present in human plasma as inert precursors and be occasionally activated by similar mechanisms.

pressive when there is considerable alteration of the plasma protein pattern, even when the coagulation defect is not very significant by laboratory tests. This suggests that the hyperglobulinemia of these patients may play a role in the pathogenesis of their bleeding tendency.

THE FIBRINOLYTIC MECHANISM (Figure 20)

There exists in the circulating plasma a pro-enzyme (profibrinolysin). The pro-enzyme is not capable of attacking any of the coagulation proteins. It may do so after being activated by bacterial filtrates (staphylokinase; streptokinase; etc.) or by tissue extracts (fibrinolysokinase) in vitro and in vivo its activation may be due to the liberation of tissue kinases (in which lung and uterine tissues are particularly rich), to the activity of bacteria, and finally, to liberation of adrenalin ("alarm reaction"). Plasma, and serum, however, contain two antagonistic agents: antifibrinolysokinase (which opposes the activation of fibrinolysin) and antifibrinolysin which quickly combines with, and neutralizes, fibrinolysin. Antifibrinolysin is able to combine with fibrinolysin, at least in vitro, according to definite quantitative proportions, the reaction being completed within sixty to ninety minutes. For this reason, and if no constant supply of active fibrinolysin is available, clot lysis is of short duration even when massive activation has taken place.

FIGURE 21—SIGNIFICANT FIBRINOLYSIS MAY BE FOUND IN THE FOLLOWING CONDITIONS

1. Hemorrhage, shock, trauma, "stress"
2. Extensive surgery (especially pulmonary, pancreatic, etc.)
3. Obstetrical accidents (abortion, premature separation of placenta(*), etc.)
4. Leukemic states
5. Parenchymal liver disease (especially cirrhosis)
6. Transfusion reactions (hemolytic, "plasma transfusion reaction")
7. Metastatic carcinoma of the prostate

* An alternative explanation postulates that thromboplastic substances of placental origin may pass into the maternal circulation and induce intravascular clotting: fibrinogen and other coagulation proteins would then be consumed and severe bleeding tendency develop. The two explanations may possibly be integrated, since activation of fibrinolysin may follow attempts to intravascular clotting, as in "plasma transfusion reaction."

Also, there is an endocrine control of the fibrinolysin-antifibrinolysin complex, which has been described in detail by G. Ungar and Damgaard.[66] In the guinea pig the spleen probably produces two opposing factors: *splenin A* which accelerates, and *splenin B* which decelerates the inactivation of fibrinolysin by antifibrinolysin. In man and in pathologic conditions of active fibrinolysis, ACTH and cortisone may quickly decrease the plasma fibrinolytic activity.[67] We have found these hormones of great therapeutic value in the control of fibrinolytic crises.

The careful control of the mechanism of activation of fibrinolysin and of the activity of the free enzyme is of extreme importance. This quickly becomes apparent when one considers the disastrous consequences of the activation of fibrinolysin, which is accompanied by very severe bleeding tendency. This is seen in a series of clinical conditions (Fig. 21). Thoracic and pancreatic surgery,[68] some of the cases of obstetrical accidents, such as premature separation of placenta, shock, severe hemorrhage, are followed by increased fibrinolytic activity. Marked activation of fibrinolysin follows an attempt at intravascular coagulation in hemolytic transfusion reaction and "plasma transfusion reaction." In leukemia and parenchymal liver disease, fibrinolysis is also present. There is some contention as to whether active fibrinolysis may destroy other coagulation proteins besides fibrin.[69] If streptokinase may be considered to activate only profibrinolysin, then our experiments with the intravenous injection of purified streptokinase- streptodornase preparations, clearly point out that this is so, although the possibility exists that kinases may activate not only profibrinolysin but precursors

of other proteolytic enzymes as well. Finally, a preformed fibrinolytic enzyme, similar to but not identical with fibrinolysin, enters the circulation in cases of disseminated prostatic carcinoma, as demonstrated by Tagnon et al.[70, 71] This enzyme destroys not only fibrin, but also fibrinogen, prothrombin and other accessory factors, inducing a most alarming hemorrhagic picture.

While fibrinolysis is a very important pathogenetic mechanism of hemorrhage in pathologic conditions, there is no definite evidence that the enzyme plays any role in the normal mechanism of blood coagulation. It has been postulated that fibrinolysin may be responsible for the initiation of blood clotting, but no clear-cut experimental evidence of this concept has been obtained. The limited activation of profibrinolysin which accompanies the coagulation of blood may be interpreted in favor of the concept that the enzyme cooperates in limiting the extension of the intravascular clot of fibrin. It is obvious, however, that our present knowledge is too limited to attempt an evaluation of the role of fibrinolysin in the normal hemostatic process.

Conclusion

Perhaps a few final remarks are in order in closing this presentation. In preparing it, I had meant to try and harmonize the many valuable contributions in the field, particularly for the past ten years, which have witnessed a veritable revival of interest and progress in the subject of hemostasis. This goal proved to be an even harder task than expected and, I rather suspect, an ungrateful one. Many unvoluntary omissions became unavoidable and I found it most difficult to prevent myself from expressing my own feelings and ideas more often than I have done. One's own work, I am afraid, generates often preconceived ideas, especially when one has behind him years of investigation, elating at times but more often frustrating, and of interpretative effort.

To prepare this presentation, however, has also been a refreshing and encouraging experience. While the multiplicity of hypotheses and the conflict of experimental findings still deny us a firm theoretical basis for the interpretation of the mechanisms of hemostasis, the impact of the advances of the last ten years on the diagnosis and management of the bleeding patient have been staggering. New diagnostic tests have greatly increased the accuracy of the diagnosis; broader interest in the isolation of coagulation factors and of platelets points to more specific methods

of treatment in the near future. One feels that, with the unending ferment of ideas and fervor of investigation in this field, great progress lies ahead.

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AN EVALUATION OF ADRENALECTOMY IN MAN: PHYSIOLOGICAL CHANGES AND THE EFFECT ON ADVANCED NEOPLASTIC DISEASE*

Eighth James Ewing Memorial Lecture

HENRY T. RANDALL

Professor of Surgery, Sloan-Kettering Institute Division of Cornell University Medical College

JAMES EWING, in whose memory this lectureship is dedicated, died on May 16, 1943, a few days short of ten years ago. His name has already joined those select few in the history of New York medicine whose contributions confer immortality. In view of the close proximity of the tenth anniversary of his death, it is appropriate to review briefly his career which significantly influenced the development of interest in cancer and cancer research throughout the country.

Dr. Ewing graduated from Amherst College in 1888 and from Columbia University College of Physicians and Surgeons, receiving his degree of Doctor of Medicine in 1891. He served an internship at the Roosevelt Hospital where one of the attending physicians on service was Dr. Francis Delafield, and it was Delafield who first interested Ewing in the laboratories.[1] It is significant and appropriate that today the two institutions of the Department of Hospitals of the City of New York devoted to the care of patients with cancer bear the names of Francis Delafield and James Ewing. Following his internship and a service in obstetrics, Ewing became an assistant in histology and later in surgical pathology at the College of Physicians and Surgeons where he came under the stimulating influence of T. Mitchell Prudden, M.D. Then in 1899, at the age of thirty-three, he became head of the Department of Pathology at Cornell University Medical School. Plagued by physical infirmities most

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From the Departments of Medicine and Surgery, Memorial and James Ewing Hospitals, and the Division of Clinical Investigation, Sloan-Kettering Institute, New York.
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of his life, and saddened by the early death of his wife, he devoted his time almost exclusively to his laboratory and to teaching which he dearly loved. Dr. Ewing's early association with Memorial Hospital began through the late James Douglas whose interest in radium and in a specialized hospital for cancer treatment led him to furnish funds for research to Memorial. Dr. Ewing became Director of Research and Pathologist to Memorial Hospital where he maintained a keen interest in clinical research, particularly in the field of radium and x-ray therapy, for a period of three decades.

The first edition of Ewing's book *Neoplastic Diseases* was published in 1918. It was based on his large experience with cancer and reviewed the entire field of the pathology of tumors. It rapidly became a classic. This work stimulated an awakening interest of both pathologists and clinicians in the field of cancer. Dr. Ewing's leadership, and his interest in specialized institutions and cooperating teams to attack the cancer problem directly, have resulted in an awakened public interest and in the development of other similar institutions, and of societies devoted to the cancer problem. It is fitting, therefore, that in this lectureship established in Dr. Ewing's name a phase of clinical investigation of cancer involving the cooperative effort of several medical disciplines be presented. It is the purpose of this paper to review the endocrine attack on cancer through total adrenalectomy and to present the present status of this investigation as conducted at Memorial Center.

The relationship between the development of the breast and of the prostate and the endocrine system, particularly the gonads, has long been known. That certain cancers derived from breast and prostatic epithelium should retain their dependency on hormones and be influenced in their growth by castration is a well documented fact and of practical clinical value in the treatment of advanced metastatic disease. The observation that following castration further beneficial effects may in some instances be obtained by the removal of the adrenal glands is relatively new, since maintenance of life following bilateral surgical adrenalectomy in man has been practical only since the general availability of cortisone as a replacement therapy.

In 1889, Schinzinger[2] proposed castration for carcinoma of the breast in women, basing his recommendations on observation of atrophy of the breasts following loss of ovarian function. In 1896, Beatson[3] performed surgical castration on two women with advanced mammary carcinoma

and observed improvement in both, with regression of their local disease. Nine years later, Lett[4] reported a collected series of ninety-nine cases of castration in women with advanced breast cancer, with marked improvement in twenty-three patients and less distinct although definite changes in thirteen more. A response rate of 36.4 per cent over-all was obtained, and of those benefited, one half were reported to have been improved for a year or more. Despite this, until recently, oophorectomy has been little used in the treatment of breast cancer, being succeeded by x-ray castration despite the fact that complete ovarian defunctionalization is less certain by this means. The introduction of testosterone in the treatment of breast cancer[5-8] and the investigations that followed further confirmed in man the hormonal sensitivity of certain of these lesions. Unfortunately, while marked regression of local and metastatic disease may occur both following castration and following androgen therapy, the duration of the favorable response is brief, and in a few months to a year or so progression again occurs in the average responsive case. About three-fourths of all cases of carcinoma of the breast do not respond objectively and one half not at all[9] to hormone therapy.

Surgical castration as a method of treatment in advanced prostatic cancer and the advantages of estrogen therapy are now well established.[10-12] However, few if any cures are obtained and while the percentage of cases likely to respond and the duration of the response are both more favorable than with breast cancer,[13] the fact remains that almost all eventually relapse. The production of androgens and estrogens by the adrenal glands in mice was demonstrated by Woolley[14] and his associates who observed female and male mice of several strains castrated between one and six months of age. They found hyperplasia and neoplastic changes of the adrenal cortex; some of the tumors exerted androgenic effects, others estrogenic. In several animals, carcinomas of the mammary glands developed as they did in normal females of these strains. These changes in the adrenals were prevented by the administration of estrogen to the castrate mice probably by pituitary inhibition. Human tumors of the adrenal with both androgenic and estrogenic effects are rare but well documented as are tumors producing a corticoid effect as manifested by Cushing's syndrome.[15]

Postulating that in patients with prostatic cancer who fail to respond to castration or in those who relapse there must be some source of androgen present other than from the testicles, Huggins and Scott[16] in

1945, reported four cases in which they had performed bilateral adrenalectomy. One patient survived for 116 days in a hypoadrenal state with perhaps some inhibition of the rate of growth of tumor. At this time it was not possible to maintain life in the surgically adrenalectomized man because of inadequate replacement therapy. Observations were made, however, that indicated the disappearance of urinary androgenic activity in this patient's urine and a marked drop in the total 17-ketosteroid excretion, leading them to the conclusion that the extragonadal androgenic depot in man was the adrenal. This conclusion implies that in those patients who responded and then relapsed there had been an alteration in adrenal function with a production of an increased amount of androgen, or of new androgenic substances. There is support for this hypothesis; indeed the adrenals may play a role in man in other neoplasms than those dependent on estrogenic and androgenic hormones. Dobriner and his co-workers[17, 18] have shown in patients with neoplastic disease not only abnormal amounts of normal compounds in the urine but also numerous compounds not normally present. These compounds are believed to be the metabolic end products of adrenal cortical activity and to indicate altered adrenal function. On the other hand it is equally possible that adaptation of the cancer itself to a new hormone balance can explain failure after a response to castration or hormone therapy, or for that matter to adrenalectomy.

When cortisone became available, several medical groups undertook further investigation of the effects of bilateral adrenalectomy on cancer and others of partial or total adrenalectomy in Cushing's syndrome and hypertension. Techniques were evolved for carrying a patient through the operative period and maintenance has proved relatively simple in the absence of major stress.[19, 20] In September, 1951, Huggins and Bergenstal[15] reported two patients with advanced prostatic carcinoma on whom bilateral adrenalectomy had been performed with clinical remission in the disease. In November of the same year[21, 22] eighteen cases were reported, seven with prostatic carcinoma, seven with mammary carcinoma —one of which was a male, and four with miscellaneous tumors. Three of the prostate cases had clinical remissions, two were reported as somewhat improved and one was unimproved. Of the breast carcinomas, three were much improved, and one slightly so. There was one death postoperatively in each of these groups. The four miscellaneous tumors were unaffected. Virtually simultaneous castration was done in three of

four female breast patients who improved.[23] Huggins and Dao[24] have recently reported an expanded series with emphasis on carcinoma of the breast. They reported fifty-five cases with two males. There were three deaths within thirty days of operation in the series, all in females. Of the fifty remaining women, twenty-five had simultaneous (within two weeks) oophorectomy and adrenalectomy and twenty-five had adrenalectomy alone. The median age of the groups on which adrenalectomy alone was performed was fifty-two, and in patients less than fifty-two in this group previous surgical or x-ray castration had been performed. In the group in which simultaneous adrenalectomy and oophorectomy were performed the median age was forty-three. Only eleven of these patients were actively menstruating prior to surgery. Ten patients in each group were reported to have significant regressions following adrenalectomy of from two months to nearly two years. The microscopic appearance of the original breast carcinomas was reported as being probably significant in prognosis. The better differentiated adenocarcinomas and papillary carcinomas showed a high incidence of response to adrenalectomy while the more anaplastic lesions in general did not respond. Of importance is the statement that response was seen in patients who had not previously responded to testosterone and ovarian irradiation. Harrison and his co-workers[25] have reported their experience with a series of seven patients adrenalectomized for carcinoma of the prostate. All seven had previously responded to orchiectomy and estrogens. Following adrenalectomy five of the seven patients had subjective relief and there was regression of the cancer demonstrated by x-ray for seventeen months in one case. All patients were continued on estrogens as well as desoxycorticosterone and cortisone postoperatively. Androgens did not completely disappear from the urine following adrenalectomy, although significant reduction occurred. Increased doses of cortisone increased urinary androgen output.

Taylor and co-workers[26] have recently reported twenty-five cases of advanced malignancy in which bilateral adrenalectomy was performed. There were one carcinoma of the ovary, six of the prostate and eighteen of the breast in this series; two of the breast cases were males. There was no response in the carcinoma of the ovary. All but one of the prostatic carcinomas showed subjective improvement for two to seven months and one of them objective improvement. Of the eigh-

teen breast cases, nine had subjective responses and five of these have shown major objective improvement including reduction in tumor size, healing of ulcerations and recalcification of bony metastases. The longest period of observation of remission was eight months.

Work begun by a group of investigators at Memorial Center in February, 1951, was reported by West et al.[27] and Hollander et al.[20] in 1952. In this initial report, two of the seven cases of carcinoma of the prostate, in relapse following castration and estrogen, showed objective evidence of improvement following adrenalectomy as did two of five patients with carcinoma of the breast. In addition certain physiologic effects of acute adrenal insufficiency were presented. Pearson et al.[28] more recently have reported from a Memorial series a total of thirty-three patients three or more months following bilateral surgical adrenalectomy. These included twelve patients with prostatic carcinoma, twelve with breast carcinoma and nine with seven miscellaneous neoplasms. Objective criteria of response were carefully established, and separated from subjective response. Pearson[29-31] and some of the group have reported new techniques for objective evaluation of response to therapy based on calcium balance in patients with osseous metastases. They also reported studies of water and salt balance during acute adrenal insufficiency. They found that calcium excretion in the urine appears to be a prompt and sensitive measurement of response in patients with osteolytic metastases following castration or adrenalectomy. High levels of excretion of calcium and markedly negative balances promptly fell and the calcium balance became positive in patients who responded. Hypercalcemia present in two patients disappeared following adrenalectomy. Calcium balance changes preceded by several weeks other objective evidence of improvement and the method promises to be of great value in the early evaluation of changes produced by various forms of therapy. The group at Memorial Center has continued the series of adrenalectomies and at this time (May 1, 1953) there are now forty-six cases on whom bilateral total adrenalectomy has been performed for advanced cancer and who have been evaluated for a period of one month or more postoperatively.

Results

I. *Miscellaneous Tumors:* Table I presents the results of bilateral total adrenalectomy in nine patients with seven different types of tumors other than cancer of the breast or of the prostate. In no instance was

TABLE I.—SUMMARY OF MEMORIAL CENTER ADRENALECTOMY CASES TO MAY 1, 1953

Type of Lesion	*Total Cases*	*Subjective Improvement*	*Objective Improvement*
Cancer of breast	20	14	8
Cancer of prostate	17	11	2
Miscellaneous	9	0	0

there evidence of any effect of adrenalectomy on these tumors.

II. *Prostate Cancer:* The results of bilateral adrenalectomy in seventeen patients with cancer of the prostate are shown in Table II. The response is divided into subjective and objective improvement. Subjective improvement is defined as relief of the most prominent symptom, most commonly pain, and was often accompanied by an increased sense of well being, increased appetite, greater ability to walk and in some instances gain in weight. Objective improvement means regression in the size of tumor masses, measured by palpation or by x-ray changes. All patients except F.M. and M.C. had been orchiectomized months to years prior to adrenalectomy, and all had received estrogen therapy. There were four deaths within thirty days of operation. Two patients were in a nearly terminal state and died three and eleven days postoperatively without direct surgical complications, and without any response to the procedure. One died of a cerebral hemorrhage on the second postoperative day, and one of a myocardial infarction on the twenty-first day. Eight patients had symptomatic improvement lasting from three weeks to seven months. The clinical improvement has in many instances been striking and appears to indicate that adrenalectomy had some effect on host-disease relationships. However, in all instances, the tumor continued to grow as evidenced by progressive x-ray changes, and there was a gradual return of symptoms. There has been no significant change in the serum acid phosphatase in any of these patients. An additional patient, M.C., was subjected to adrenalectomy prior to castration. He had a transitory subjective response lasting two weeks, followed by a relapse and on castration five weeks after adrenalectomy he has had a subjective improvement which still continues thirteen months later. Two other patients have had both subjective and objective response. Patient T.H. had a large mass arising from the prostate, filling the pelvis and

TABLE II.—RESULTS OF ADRENALECTOMY IN PROSTATE CANCER
(AS OF 5/1/53)

Patient	*Survival Days*	*Duration of Improvement*		*Present Status*	*Cause of Death and Remarks*
		Subjective Days	*Objective Days*		
L.M.	2	0	0	Dead	Cerebral Hemorrhage
J.A.	3	0	0	Dead	Cancer
R.G.	11	0	0	Dead	Cancer
F.M.	21	0	0	Dead	Myocardial Infarction
F.H.	33	21	0	Dead	Cancer
M.N.	44	0	0	Dead	Cancer
M.B.	124	30	0	Dead	Cancer
I.B.	128	90	0	Dead	Adrenal Insufficiency
T.H.	133	30	133	Dead	Unknown? Adrenal Insufficiency
W.S.	196	150	0	Dead	Cancer
A.B.	201	60	0	Dead	Cancer
J.W.	294	220	0	Dead	Cancer
N.T.	170	81	0	Living	Progressive Disease
H.L.	58	0	0	Living	Progressive Disease
J.S.	128	128	128	Living	In Remission
J.R.	107	107	0	Living	In Symptomatic Remission
M.C.	440	14	0	Living	Castrated — 5 Weeks After Adrenalectomy; in Remission

palpable masses in both lower quadrants. Six weeks after adrenalectomy, all observers agreed that there had been significant regression of the masses. He died 133 days after adrenalectomy in another city of an obscure cause, possibly adrenal insufficiency, and at postmortem only three minute tumor masses were found, one in the prostate, and two near the junction of the ureters and bladder. There seems no doubt that there was marked shrinkage of this patient's lesions. The other patient, J.S., has a carcinoma of the prostate with osseous metastases. Following adrenalectomy there has been definite decrease in the size of his prostatic tumor mass with improvement in his urine flow. There is also relief of bone pain with improved walking and increased appetite. Most recent x-rays, however, show new osteoblastic lesions, and he may represent

simultaneous progression of bony lesions with regression of soft tissue tumor. There were two patients with no response to adrenalectomy.

It seems probable that at the present stage of development, bilateral adrenalectomy does not offer a practical form of therapy for advanced prostatic carcinoma. Although a case may be made for the high incidence of symptomatic relief obtained, the limited subjective effect and the short duration of response make its usefulness doubtful. However, certain lines of further investigation are suggested.

It has been impossible to maintain life in man following bilateral adrenalectomy without the use of cortisone or hydrocortisone. Desoxycorticosterone and salt, in contrast to their usefulness in experimental animals, are ineffective. Cortisone and hydrocortisone are metabolized in man into at least one end product which is androgenic. This substance is 11-OH-androsterone.[28] Harrison and his coworkers[25] have also reported a rise in urinary androgen in adrenalectomized males with increasing doses of cortisone. Thus replacement therapy may prevent achieving the objective of adrenalectomy in removing androgen from the patient. Some of our group[32] have demonstrated that corticosterone is capable of maintaining life in bilaterally adrenalectomized patients, and since it does not appear to be metabolized into the usual neutral ketosteroids, its end products may not be androgenic. Further study of this problem is continuing at the present time. Another possible source of androgen lies in accessory adrenal tissue to be found in the region of the celiac plexus and possibly elsewhere in the body. Graham[33] made a careful search in 100 consecutive autopsies of the area of the celiac plexus and in 32 per cent of the cases found accessory tissue. These deposits averaged 7 by 4 by 3 mm. in size. Thus bilateral adrenalectomy probably does not represent total adrenalectomy in many patients. Cortisone withdrawal studies, in eight of nine patients, however, have produced prompt acute adrenal insufficiency, and in no instance has there been a response to corticotropin.[20] Hypophysectomy seems the logical approach completely to suppress adrenal function.

III. *Carcinoma of the Breast:* The results of adrenalectomy in twenty patients with carcinoma of the breast are presented in Table III. The same division into subjective and objective response and the same criteria were used as in prostate cases. In addition, calcium balance studies were carried out on many patients with osteolytic lesions, and a change from a markedly negative to a positive balance was considered

TABLE III.—RESULTS OF ADRENALECTOMY IN BREAST CANCER (AS OF 5/1/53)

Patient	*Survival Days*	*Duration of Improvement* *Subjective Days*	*Objective Days*	*Present Status*	*Cause of Death and Remarks*
P.K.	18	0	0	Dead	Cancer and Bronchopneumonia
A.J.	0	—	—	Dead	Cardiac Arrest
R.G.	74	0	0	Dead	Cancer
R.L.	100	30	0*	Dead	Cancer
A.C.	119	14	0	Dead	Cancer
S.B.	121	60	0*	Dead	Cancer
M.D.	170	21	0	Dead	Cancer
B.Mc.	122	90	0	Dead	Cancer
E.H.	78	0	0	Living	Evaluation Equivocal
B.M.	76	0	0	Living	Remission From Cortisone
M.Des.	49	49	0*	Living	Progressive Disease
M.M.	65	0	0	Living	Progressive Disease
L.K.	228	120	120	Dead	Cancer
G.M.	390	120	120	Dead	Cancer (Transient Remission with Androgen)
V.Y.	353	353	353	Living	In Remission
M.L.	177	177	177	Living	In Remission
G.B.		(173)	(173)	Living	In Remission (Androgen Added For 3 Mos. 1 Mo. P. Adrenex.)
K.H.	100	100	100	Living	In Remission
M.C.	92	92	92	Living	In Remission
V.E.	30	30	30	Living	In Remission

* Regression of skin and bone metastases with simultaneous progression of liver metastases.

objective evidence of improvement. All patients with the exception of M. Des. had surgical castration at least six weeks prior to adrenalectomy, and the clinical response to oophorectomy was carefully evaluated, adrenalectomy being done only when there was unequivocal evidence of progression of disease (See Table IV). M. Des. had received more than 2000r ovarian dose and had a marked radiation reaction of the suprapubic skin. The age distribution of the patients in this series is from twenty-four to seventy-three, the mean age is 44.6 and the median age forty-four. The youngest patient to show objective improvement is thirty-one and the oldest fifty-two. Two patients died within thirty days of operation. One, A.J., was a seventy-three year old woman with mas-

TABLE IV.—RESPONSE OF PATIENTS WITH BREAST CARCINOMA TO ANDROGEN, CASTRATION AND ADRENALECTOMY

Patient	*Age*	*Disease Onset of*	*Time* Of Androgen* B	*Response To Andogen* B	*Time* Of Castration*	*Response To Castration*	*Response To Adrenalectomy*
G.M.	41	5 Years 7 Months	27 To 17 Months	+	14½ Months	+	+
L.K.	50	5 Years	19 To 13 Months	+	10½ Months	+	+
M.L.	52	2 Years 2 Months			7 Months	+	+
V.Y.	44	2 Years 10 Months	8 Months To 12 Days	0	18 Months	P	+
K.H.	31	6 Years 10 Months	10-8 Months 6-4 Months	+	5 Years 8 Months	P	+
M.C.	44	6 Years 1 Month	0		2 Years 8 Months	P	+
V.E.	51	3 Years 11 Months	0		3 Years	P	+
B.Mc.	49	5 Years 7 Months	23 To 2 Months	+	3 Years 11 Months	P	0
M.M.	43	1 Year 10 Months	13-11 Mos.	+	5 Months	+	0
S.B.	41	2 Years 7 Months			7 Months	+	0**
R.L.	45	9 Years 10 Months	24 To 15 Months	0	9 Years	P	0**
M.Des.	34	2 Years 11 Months	1 Yr. 11 Mo. To 0	+	1 Year 11 Months (X-ray)	+	0**
A.C.	24	1 Year 5 Months	5 To 2 Months	0	7 Months	0	0
M.D.	54	1 Year 2 Months			47 Days	0	0
R.G.	47	3 Years 1 Month			46 Days	0	0
G.B.	42	5 Years 2 Months			3 Years 4 Months	P	0
E.H.	47	1 Year 11 Months	0		1 Year 2 Months	P	0

* Prior to adrenalectomy
** Regression of skin and bone metastases with simultaneous progression of liver metastases
P = Prophylactic

sive intra-abdominal metastases and ascites, who died of cardiac failure two hours after cardiac arrest and resuscitation during surgery. The other, P.K., died eighteen days after operation of bronchopneumonia complicating extensive metastatic breast cancer. Subjective response was seen in fourteen of the remaining eighteen patients. It consisted of definite relief of the dominant presenting symptom, usually pain, and was equally as dramatic as the responses seen in the prostate cases. One

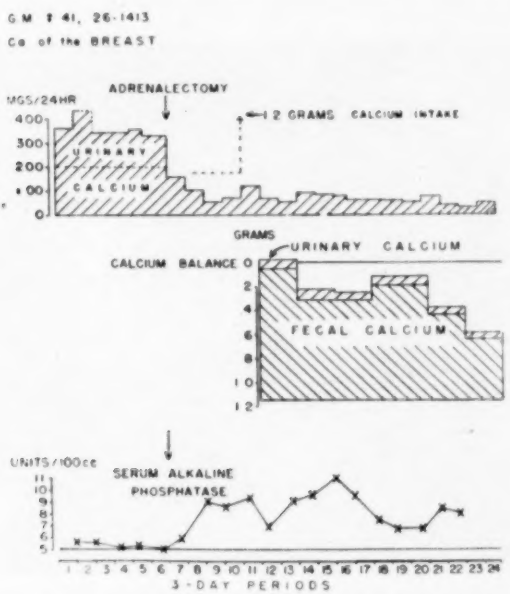

Fig. 1—Calcium balance data in patient G. M. Upper figure shows urinary calcium excretion before and after adrenalectomy. Central figure is balance data, intake is plotted down from the zero line, and output superimposed upward. (From Ref. 28; Pearson, O. H. et al., *Surgery 34*:543-55, 1953. Reprinted by permission.)

of these cases, G.B., has had both a subjective and an objective remission following adrenalectomy. This patient was given androgen for a period of three months starting one month postoperatively. She had extensive metastases involving the spine and while some relief of pain was noted post-adrenalectomy she continued to have spasmodic crampy pain in her thighs. She was also given x-ray therapy to the spine, and so can not be evaluated for this series beyond one month post-adrenalectomy. Excluding this case, seven of thirteen patients who had subjective improvement also exhibited objective improvement. Five patients are in remission at the present time from one month to one year after adrenalectomy. Two other patients had remissions of four months with objective improvement followed by relapse, and both are now dead of cancer. Of the two patients who have died, patient G.M. showed extensive osteolytic metastases and in addition had two small recurrent nodules in her mastectomy scar on the right. The calcium metabolism

Fig. 2a (front)—Patient V. Y. photographed 5/7/52, one week before adrenalectomy.

Fig. 2b (back)—Patient V. Y. photographed 5/7/52, one week before adrenalectomy.

data on this patient are shown in Figure 1 from Pearson's paper[28] to illustrate this method of objective evaluation. It will be noted that for eighteen days prior to adrenalectomy the patient was in markedly negative calcium balance. Under these conditions hypercalciuria is indicative of bone destruction and is considered to reflect the growth of osteolytic metastases. Immediately after adrenalectomy there was a sharp drop in urinary calcium excretion, and subsequently, on increased intake, the balance became markedly positive. Also shown is the increase in alkaline phosphatase which is consistent with increased osteoblastic activity. Urine calcium levels remained within normal limits for four months and skeletal x-rays showed no significant change. The two skin nodules, one of which was biopsied, regressed until they were no longer detectable six weeks after adrenalectomy. Back pain returned at four months, and hypercalciuria at six months. A transitory remission was obtained with androgen and the patient died 390 days post-adrenalectomy. Patient L.K. had a marked hypercalciuria which similarly returned to normal following adrenalectomy. This is the patient in whom cortisone withdrawal failed to precipitate an acute adrenal insufficiency, although she developed marked pigmentation over a six weeks period and it is interesting to speculate that she probably had accessory adrenal tissue. Unfortunately a postmortem was not obtained. Of the five surviving patients with objective evidence of improvement, two, V.Y. and V.E., have had measurable regression of soft tissue metastases, while in three, M.L., K.H., and M.C., the evidence is based on calcium balance studies. Patient V.E. has had a two-thirds regression in size of a left second interspace parasternal recurrence in one month post-adrenalectomy. Patient V.Y. has had major regression of extensive chest wall recurrent disease. Photographs taken on admission in May, 1952, and those taken April 13, 1953, are shown in Figures 2 and 3. This patient was forty-five years of age when first seen and had had a right radical mastectomy twenty-one months previously for infiltrating duct carcinoma Grade II with extensive axillary metastases. The lesion had appeared two months after delivery of a child. Because of the poor prognosis, a prophylactic x-ray castration was done, and she was given x-ray therapy to the local area. Nine months later nodes were palpated in the infrahyoid area on the right and a node dissection done but all the nodes were negative. Eight months before adrenalectomy a small mass appeared in the suprasternal notch, to be followed within one month by

Fig. 3a—Patient V. Y. photographed 4/13/53, eleven months post-adrenalectomy. Linear scars on chest wall are biopsy sites. (front)

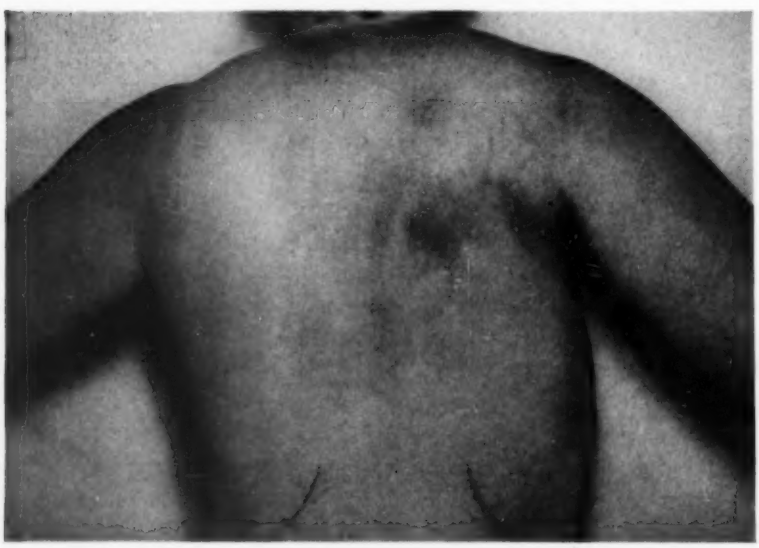

Fig. 3b—Patient V. Y. 4/13/53, eleven months post-adrenalectomy. (back)

the explosive eruption of multiple nodules in the skin of the chest wall, the right neck and the scapular area. The patient was placed on testosterone 300 mgm. per week and small doses of local x-ray were given, both without effect. When first seen in March, 1952, she had rapid progression of her lesions, complained of nausea, anorexia, and had had an eight pound weight loss. There was brawny edema of the right arm. Because she had not had a surgical castration, it was advised that this be done and it was done by her referring surgeon on March 25, 1952. The ovaries were small and atrophic. Within a month it became obvious that the local lesions were continuing to expand, and nausea, vomiting and weight loss continued. The testosterone was continued until April 30th, then stopped without change in gastrointestinal symptoms. Accordingly, on May 12, 1952, the patient was subjected to bilateral adrenalectomy through two flank incisions. There was extensive involvement of the retroperitoneal para-aortic nodes with carcinoma and there were two metastases in the right gland, the left was normal. The postoperative course was uneventful. Her gastrointestinal symptoms disappeared at operation and have not returned. Regression of the skin nodules was first noted one month after adrenalectomy and they rapidly regressed until at nine months only one tiny nodule was palpable. At eleven months, this lesion had increased slightly in size, but the patient has no other symptoms. Repeated biopsies of the chest wall have consistently shown the presence of carcinoma cells. It might be that testosterone exerted a consistently unfavorable effect in this patient, and that its withdrawal resulted in regression, but it seems more probable that adrenalectomy was responsible for the improvement shown.

Three patients have shown subjective improvement together with a shift of calcium balance to normal from hypercalciuria, and in one case hypercalcemia. Two of the three had regression of skin nodules. At the same time, they have demonstrated progressive growth of liver metastases. A switch to parenteral cortisone in one of these patients did not affect the growth of the liver disease. These patients, R.L., S.B., and M. Des., are counted as objective failures. This paradoxical behavior is hard to explain. In six patients the disease has continued to progress unabated despite symptomatic response and in one case, B.M., hypercalciuria returned three weeks after adrenalectomy and she went into adrenal crisis. On a high level of cortisone, 300 mgm. for several days and maintained on 200 mgm. per day, she has apparently gone into remission

again. It seems reasonable to assume that adrenalectomy has eliminated some steroid or other substance produced by the adrenal cortex that in some cases was contributing to the growth of the cancer. Pearson, West and Treves[24] have just reported studies which indicate that there may be two types of mammary cancer, one dependent on estrogen for maintenance of growth, and the other non-dependent. Table IV presents the correlation between response to castration and the objective response to adrenalectomy in seventeen patients of this series. It will be noted that except for the three patients with paradoxical behavior of liver metastases, the patients who responded to castration responded to adrenalectomy, and the reverse holds true as well. If it is so that there are two types of breast carcinoma, one of which is independent of the presence of estrogen, then it would follow that estrogen is the substance which has been removed by adrenalectomy to produce remission.

IV. *Effect of Cortisone on Metastatic Cancer:* The effect of cortisone as such on breast and prostatic carcinoma must be considered. Harrison and co-workers[25] have reported nine cases of carcinoma of the prostate treated with an initial dose of 100 mgm. per day followed by 25 to 37 mgm. a day for one to three months. All but one patient had an increased sense of well being and some relief of pain, but there were no objective changes. There was a fall in 17-ketosteroid excretion in all patients. One patient treated with 100 mgm. per day for three weeks had relief of pain and a fall in acid phosphatase levels. In the Memorial experience, one patient who had carcinoma of the breast and was inoperable was treated with cortisone with transitory and slight subjective improvement. Another, with osseous metastases from breast carcinoma was castrated recently, and following castration developed hypercalciuria and hypercalcemia (18 mgm. per cent) with coma. On large doses of cortisone (300 mgm. per day) her blood calcium promptly fell to a low level, and her urinary calcium dropped from 900 mgm. per day to 50 mgm. per day. She is still in remission seven weeks later. Two patients in the breast series presented have also responded to cortisone. M. Des. was bedridden with nausea and vomiting and a serum calcium of 12.8 mgm. per cent. Placed on 300 mgm. of cortisone per day for ten days, then 200 mgm. per day, she was able to get out of bed and to eat within forty-eight hours, and when first seen at Memorial Hospital two and a half weeks later had a serum calcium of 8.9 mgm. per cent and a low urinary calcium excretion. This patient has extensive osseous

metastases, as well as hepatic metastases. A second patient, B.M., had hypercalciuria from osteolytic breast carcinoma metastases. Following adrenalectomy her urinary calcium fell to normal levels for about three weeks, then rose again while on 50 mgm. of cortisone per day. On high levels of cortisone, 200 mgm. per day, her urinary calcium excretion has again returned to normal and she is in remission. Informal conversation with other groups of workers indicates that several are evaluating cortisone therapy and certainly further work is indicated in this field.

V. *Metabolic Studies:* Detailed studies of the physiologic effects of bilateral adrenalectomy in man have been[20] and are being published[31] in separate communications, and some studies have been reported by others.[35, 36] Adrenalectomized patients are well maintained on oral cortisone alone in most instances. In only two of forty-six cases has desoxycorticosterone been required for control of positional hypotension, and one of these patients, V.Y., required it only for one month. The average dosage of cortisone is 50 mgm. per day, administering 25 mgm. every twelve hours. Some patients complain of weakness and anorexia unless they take 75 mgm. per day. Additional salt is not given routinely but is probably indicated in hot weather. Salt is not restricted. On this regimen the patient tolerates mild stress such as an upper respiratory infection quite well but severe infection or surgery requires much larger amounts of cortisone, comparable to the regimen used at the time of adrenalectomy. In the event of an acute crisis, the intravenous free form of cortisone should be given. Withdrawal of cortisone from surgically adrenalectomized patients under controlled conditions in a metabolic unit has shown a pattern different in rate of development and perhaps fundamentally different from human Addison's disease and from the effects of adrenalectomy on experimental animals. Loeb[37] described the syndrome of salt loss, dehydration, falling blood pressure, prostration, nausea and vomiting seen in Addison's disease in crisis, and documented the lowered serum sodium, elevated potassium, and the response to sodium chloride administration in man. He also described experimental work in dogs demonstrating the rapid loss of large amounts of salt in the urine following adrenalectomy, and the protective effect of desoxycorticosterone, salt and potassium administration. Thorn[38] described these phenomena together with a markedly diminished diuresis under water load, a low blood sugar and high insulin sensitivity, lymphoid hyperplasia and pigmentation as clinically found in adrenal insufficiency.

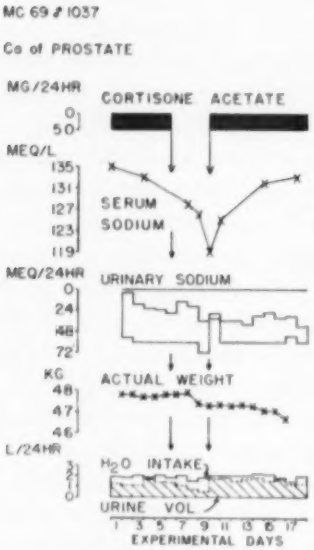

Fig. 4—Patient M. C. Cortisone withdrawal study. Note water retention and drop in serum sodium with positive sodium balance in withdrawal phase, followed by diuresis.

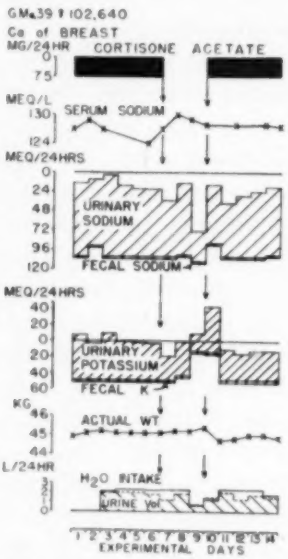

Fig. 5—Patient G. M. Balance studies during cortisone withdrawal and development of acute adrenal insufficiency. Weight gained and sodium balance remains positive during withdrawal. Potassium is not retained. Diuresis follows readministration of cortisone.[21]

In surgically adrenalectomized patients, collapse occurs much more quickly than on salt withdrawal in the Addisonian. Within twenty-four hours the patient complains of malaise, weakness, anorexia and lethargy. In forty-eight hours the weakness is profound, and by seventy-two hours the patient is usually unable to take food, and nausea, vomiting, diarrhea and stupor ensue. The blood pressure falls but not to shock levels as long as the patient is horizontal. The skin is cold and dry; the patient gaunt and ashen in appearance. Administration of cortisone results in rapid and dramatic recovery which is virtually complete in twelve hours. In these patients the serum sodium tends to fall, without loss of sodium from the body. The urine volume falls, and in seven withdrawal studies done, water retention was the most commonly observed metabolic event. Urinary sodium loss was absent in four of the seven studies and in four, significant hyponatremia developed unexplained by sodium loss. Potassium retention was not observed in five patients in whom it was studied.

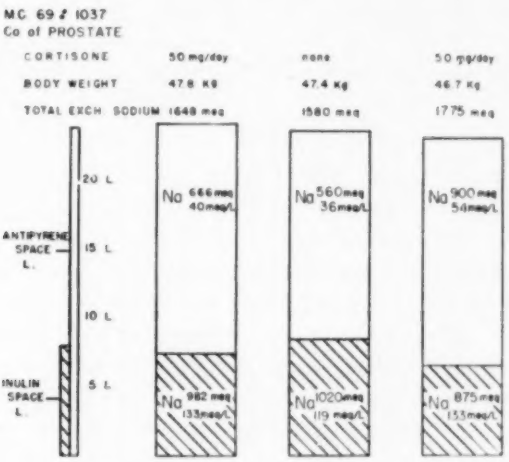

Fig. 6—Patient M. C. Antipyrene and inulin space and sodium 24 dilution before, during, and after cortisone withdrawal. The inulin space increases during insufficiency.[31]

Serum potassium levels remained normal in six patients. There was apparent expansion of the inulin space by 15 to 21 per cent in two patients so studied.[31] Hypoglycemia failed to develop even in the late stages of acute adrenal insufficiency. Internal fluid shifts and antidiuresis with the development of a syndrome resembling water intoxication together with interference with other unmeasured metabolic functions seem to be dominant in these cases. In all cases, on re-administration of cortisone a diuresis with loss of from one to 3 kg. body weight resulted.

The clinical implications are that this form of adrenal insufficiency should not be treated with large amounts of intravenous water and salt but rather that intravenous cortisone or hydrocortisone be given, together, if necessary, with support of blood pressure with vasoconstrictors and perhaps a blood transfusion.

Figures 4, 5, 6 and 7 illustrate from Mendelsohn's and Pearson's studies[31] the effect of cortisone withdrawal in patient M.C., a post-adrenalectomy prostatic carcinoma, and G.M., an adrenalectomized carcinoma of the breast. Sodium intake is plotted downward from the line and urinary output superimposed upward so that empty space below the line represents positive balance. Note that sodium balance was posi-

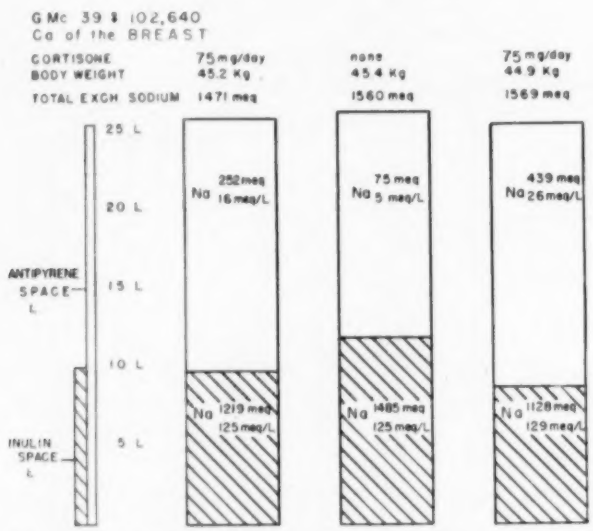

Fig. 7—Patient G. M. Antipyrene, inulin and sodium 24 diffusion space. The marked increase in inulin space and increase in antipyrene space are evident during insufficiency with rapid restoration to normal.[21]

tive in both patients throughout the test periods (Fig. 4, 5). Patient M.C. showed a sharp fall in serum sodium (Fig. 4) together with an increase in the inulin space (Fig. 6) while G.M., whose serum sodium was low initially showed little concentration change (Fig. 5) but a definite increase in the inulin diffusion space (Fig. 7). The assumption is made that extracellular sodium concentration is the same through the space available to inulin diffusion in drawing these charts. It is recognized that the definition of extracellular fluid is subject to considerable controversy and that this assumption may not be correct.

Summary

1. Bilateral adrenalectomy for advanced cancer in man is under study by several groups of investigators. The rationale and reported cases to date are reviewed.

2. Bilateral adrenalectomy has been performed on forty-six patients with inoperable cancer at Memorial Center between February, 1951, and April, 1953. These include seventeen cases of carcinoma of the

prostate, twenty cases of cancer of the breast and nine patients with various other inoperable tumors.

3. There was no response in any of nine patients with cancer other than breast or prostate.

4. Of seventeen cases of carcinoma of the prostate, subjective improvement of from two weeks to seven months was seen in eleven. Two of these patients also had objective evidence of improvement, both in soft part lesions; one of these is still alive and improved.

5. Adrenalectomy with present postoperative maintenance regimens involving the use of cortisone does not appear to be a practical therapeutic tool for carcinoma of the prostate.

6. Of twenty patients with carcinoma of the breast subjected to adrenalectomy, all but one were surgically castrated at least six weeks prior to adrenalectomy. In this group there were fourteen patients with subjective improvement of from two weeks to one year duration. Eight patients showed objective improvement. One patient has had a major regression of metastatic disease and is still asymptomatic at one year. Seven others have shown objective evidence of improvement, four of whom are in remission to six months. Two are dead after four months of objective improvement followed by relapse, and one in remission on androgen and x-ray therapy. Six patients did not respond to adrenalectomy, but one of these has responded to high levels of cortisone dosage after adrenalectomy. While further study is indicated, adrenalectomy may be considered as a possible additional means of temporary control of advanced breast cancer, particularly in cases which have shown a response to castration.

7. In this series of breast patients, those who previously responded to castration appear to have responded objectively to adrenalectomy with the exception of those with liver metastases.

8. Metabolic studies of the effect of withdrawal of cortisone maintenance in adrenalectomized patients are presented. These patients failed to show major salt losses and suggest a modified concept for the treatment of this form of acute adrenal insufficiency in man.

Addendum

As of December 1, 1953, thirty adrenalectomies had been performed for patients with carcinoma of the breast with metastases. Of these, twelve or 40 per cent, have given objective evidence of response. The average response period is nine months, the longest survivor without

relapse is now fourteen months. Patient V. Y. developed cutaneous recurrence in June of 1953, osseous disease in August, 1953, and died on November 6, 1953.

Studies of this scope, involving several medical disciplines are the result of the combined efforts of a team of investigators. This team includes Drs. Olaf H. Pearson, Norman Treves, C. D. West and Willet F. Whitmore. The auther wishes to acknowledge the privilege of acting as spokesman for this group in presenting in this lecture the present status of the work done at Memorial Center.

Many others have contributed valuable advice and assistance including Drs. Rulon W. Rawson, Frank E. Adair, Alexander Brunschwig, Joseph Farrow, William W. Daniel, George C. Escher, James Green, Jerome A. Urban, Mortimer L. Mendelsohn, John H. Tuohy, Dorothy Sved, and Helen Q. Woodard, Ph.D.

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SUBCORTICAL PARIETAL LOBOTOMY FOR RELIEF OF PHANTOM LIMB SYNDROME IN THE UPPER EXTREMITY: A CASE REPORT*

J. Lawrence Pool and Thomas J. Bridges

The cramping burning pain and distressing sensations of limb distortion which characterize a phantom limb syndrome are notoriously difficult to treat. Drug addiction frequently becomes an added problem.

Treatment of the phantom limb syndrome by alcohol injection, excision or percussion[1] of the stump neuroma often fails to provide relief. Posterior cordotomy[2, 3] and sympathectomy[4] are likewise not always beneficial although spinothalamic tractotomy is usually effective, especially for a painful phantom of the lower extremity.[5] For relief of phantom pain in an upper extremity, even a high cervical cordotomy may prove ineffective, as it did in the case to be presented. If another spinal cord operation or tractotomy at the medullary[6] or mesencephalic level is refused, it may then be necessary to consider an intracranial procedure such as unilateral[7] or bilateral lobotomy,[8] topectomy[9, 10] or resection of contralateral sensory cortex.[11-15]

These intracranial procedures however are not always of lasting benefit in such cases. For example, unilateral prefrontal lobotomy, conservative bilateral topectomy,[9] or resection of the contralateral primary sensory cortex in the experience of the authors sometimes relieves a phantom limb syndrome for only five or six months. Bilateral frontal lobotomy moreover may adversely alter the personality of the patient, while resection of post-central sensory cortex may lead to frequent convulsive seizures. Ablation of secondary or "associative" sensory cortex in addition to primary sensory cortex has proved effective in two cases[16] but not in another,[17] perhaps because the cortical resection was not sufficiently large.

In the present case frontal lobe surgery was declined on the grounds

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of possible personality change, and an additional tractotomy was refused because of possible paralysis. A generous subcortical "undercutting"[18] of the parietal association cortex representing the phantom limb was therefore proposed in the hope of alleviating awareness of phantom pain without a personality change or convulsive seizures. Since the non-dominant cerebral hemisphere was to be operated upon, speech disturbances were not expected.

The rationale of this procedure was based largely on laboratory data which at the time indicated that integrative function of the parietal cortex depended principally on its cortico-thalamic connections.[39] It was therefore expected that interruption of these fibers by subcortical parietal lobotomy would reduce awareness of the contralateral extremity by producing a Gerstmann phenomenon,[20, 21] and thus afford relief of phantom pain.

Case Report

A sixty-six year old widow admitted to the Columbia-Presbyterian Medical Center in March 1952 complained of severe constant pain in a phantom left upper extremity of five months' duration. The pain was burning and cramping in nature, shifted from hand to arm to shoulder, and was accompanied by sensations of disagreeable heaviness and postural alterations of the phantom fingers, wrist, elbow and shoulders. Discomfort was not controlled by 150 mgm. of demerol, 18 mgm. of morphine, or by 20 mgm. of pantopon given singly or in combination every three hours.

Radical mastectomy had been performed in 1945 for carcinoma of the left breast and disarticulation of the left arm at the shoulder was performed in October 1951 because of advanced lymphedema leading to gangrene of the digits. The arm was also paralyzed by extension of carcinoma into the brachial plexus.

The first component of phantom distress began three days after amputation as a cramping, heavy aching pain in the fingers, and on the fifth postoperative day a burning pain together with distressing posturing sensations afflicted the entire phantom extremity. This syndrome persisted despite intensive x-ray therapy to the carcinoma-involved left brachial plexus. In July 1951 a high cervical spinothalamic tractotomy at another hospital proved ineffective because the sensory level dropped to T-2.

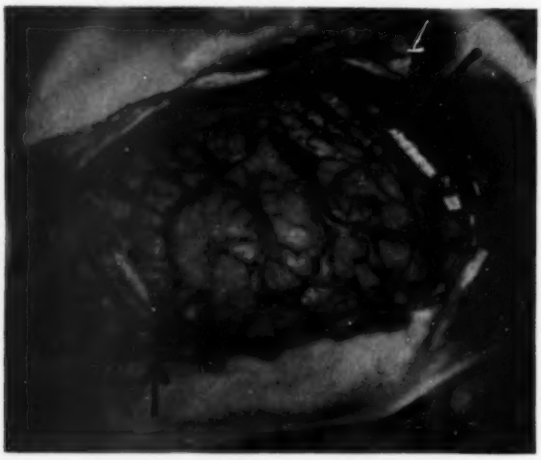

Figure 1.—Right parietal cortex after completion of subcortical parietal lobotomy. Arrow in left lower corner points to transcortical incision (at occipito-parietal junction) through which the cortical undercutting was done. Arrow at right upper corner indicates motor cortex also marked by white paper tickets. The area which has been undercut is outlined by the black thread on the cortex.

Cranial Operation: On March 13, 1952 a right parietofrontal craniotomy was performed to permit undercutting of the right parietal cortex under intravenous sodium pentothal and intratracheal nitrous oxide-oxygen anesthesia.

Protection of motor fibers from the leg area was facilitated by introducing small needles through the primary sensory area after the motor cortex had been outlined by electrical stimulation.[22] The needles, introduced perpendicular to the cortical surface for a distance of 2.5 cm., or 0.5 cm. beyond the deepest extent of the gray matter, thus prevented the cutting spatula from reaching the motor leg fibers. A 2.0 cm. transcortical incision was then made 7.5 cm. posterior to the central fissure through which undercutting of the bulk of the parietal cortex was accomplished 2.5 cm. below its surface. Most of the primary sensory cortex was also undercut. The width of the subcortical lobotomy measured 5.0 cm. close to the central fissure and 3.0 cm. at the site of the trans-cortical incision. (Figs. 1 and 2.)

Course: For six weeks the postoperative course was stormy because

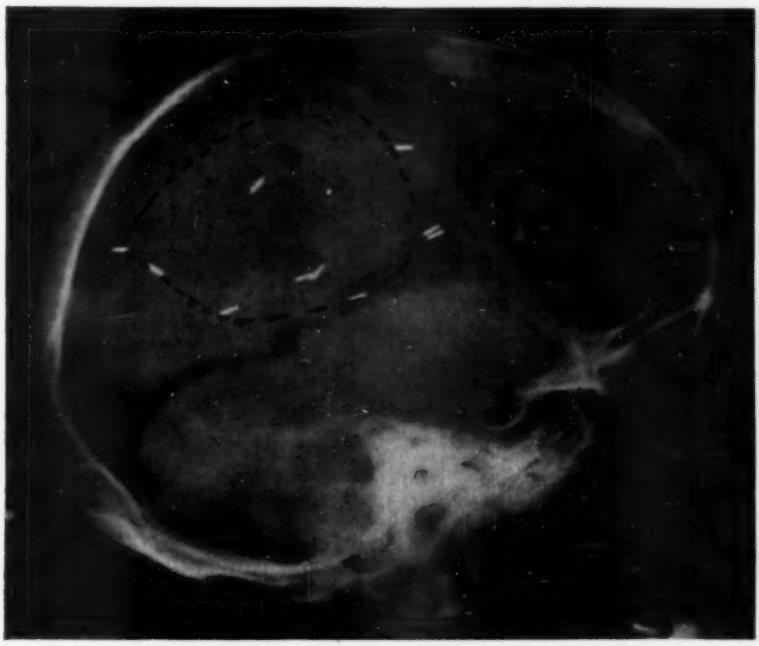

Figure 2.—Postoperative x-rays showing position of bone flap. Subcortical silver clips indicate the extent of the subcortical parietal lobotomy, which is also outlined by ink dots. Presumably the uppermost middle clip moved since operation, since the undercutting was carried within 2 cm. of the midline at operation, as shown by the ink marks.

of protracted drug withdrawal symptoms accompanied by resultant mental depression. Temporary paralysis of the left leg for ten days was followed by progressive return of power to almost normal strength by the fourth postoperative week. Impaired position sense in the left leg, plus the absence of the left arm, which otherwise would have permitted the use of a cane, prevented walking without support. No urinary or fecal incontinence occurred at any time. On the fourth postoperative day a left facial convulsive seizure occurred, but there were no subsequent seizures.

At no time were any significant reflex changes elicited and no abnormality in passive resistance was noted except for flaccidity of the left lower extremity while it was temporarily paralyzed. During this interval

a transitory left homonomous hemianopsia was present, which disappeared by the fourth postoperative week.

During the first five weeks after operation there was no sensation whatever of the phantom limb but some pain was experienced in the left anterior chest region and the left side of the neck due to the local presence of carcinoma. By the sixth postoperative week the patient began to suffer occasional twinges of pain in the digits of the phantom hand but no longer had cramping, burning or posture pain or the preoperative feeling of heaviness. Four months after operation she became aware of the phantom extremity again although there was no sense of phantom discomfort. The twinges of pain became less, and she required no medication save for nocturnal sedation. According to friends, relatives, and the patient herself, her personality remained intact. After discharge to her home she was able to read extensively, enjoy television programs, and resume the management of her business affairs. This state persisted until June 1953, over a year since craniotomy, at which time the effects of skeletal metastases became troublesome.

An electroencephalogram on March 14, 1953 was reported by Dr. Paul F. A. Hoefer as follows: The record is basically disorganized with a distinct right preponderance and shows, in addition, a large slow wave focus over the right side with bursts of slow activity over the temporal, parietal and occipital areas at varying times. Impression: Large right temporo-parieto-occipital focus.

Neurological examination in April 1953 revealed that extinction phenomena were present for pinprick over the left side of the face, head, pharynx, oral cavity and from C-2 to T-2 dermatomes inclusive on the left. (Below T-2 the previous cordotomy had already abolished pain and temperature perception.) There was no impairment of pinprick perception of pain above T-2 except on extinction tests, and no impairment of temperature perception above T-2.

Object recognition, touch and pinprick localization were normal in the face but two point discrimination was impaired over the left side of the face and neck, the calibre distances on the left being twice those on the right. Position sense was absent in the left toes, and although reduced in the left ankle, knee and hip joints, was adequate for orientation of the left leg in space. Body schema remained intact as to right and left sides, and the motor power of the left lower extremity was almost equal to that of the right. No abnormal reflexes were elicited.

Discussion

The therapeutic aspects of this parietal undercutting have been highly satisfactory, and the theoretical aspects interesting.

Therapeutically, phantom pain has been practically abolished for over a year, while pain that might have been expected from the carcinomatous nodules in the left side of the neck has apparently been dulled.[23] Drug addiction was overcome despite our initial mistake in cancelling narcotics too abruptly after operation. Personality was not altered, incontinence never occurred, and no convulsions were experienced other than the single brief left facial seizure four days after craniotomy. Both the patient and her family moreover have been extremely pleased by the effects of this operation, despite temporary weakness of the left leg which probably could have been avoided had the undercutting been less radical close to the leg area.

The fact that drug withdrawal symptoms were unusually prominent is a postoperative feature that differs in this respect from most unilateral prefrontal lobotomies although each operation sacrifices approximately the same amount of white matter. This observation, together with the lack of postoperative personality changes indicates that subcortical parietal lobotomy differs from a unilateral frontal lobotomy and thus suggests that in man these two regions of the brain may not be entirely "equipotential," despite suggestions to this effect.[24, 25]

That some reduction of contralateral body awareness occurred, and pain to some degree,[23] is not surprising in view of the observations of Gerstmann[21] and Bender.[20] Of greater interest is the fact that several weeks after operation there was some return of awareness of the phantom hand. This indicates that body memory for the phantom limb was not completely destroyed, and that some re-integration of neural patterns occurred to restore these sensory "memories." Perhaps re-integration was possible by virtue of the remaining cortico-cortical connections, a possibility suggested by the recent work of Chow[26] showing that multiple trans-cortical parietotemporal transections produce essentially the same deficits in trained macaques as cortico-thalamic interruption of the same cortical area (although neither procedure alone leads to permanent changes in the macaque). A dual system for neural integration and transmission therefore seems possible: 1) cortico-cortical or 2) cortico-subcortical.

Sensory representation in parts of the brain other than parietal

cortex, such as the premotor area[27] might also account for the return of phantom limb awareness in our case.

Altogether the observations following parietal undercutting indicate that parietal thalamo-cortical circuits are of prime importance in the maintenance of a phantom limb syndrome, as suggested by others.[13,28,29] Such a theory moreover does not necessarily exclude a psychogenic origin for phantom limb sydrome as suggested by Kolb[14] and the case of Li and Elvidge.[30] Whether a phantom syndrome be psychogenic, or neurogenic (due to a painful neuroma),[31] the contralateral parietal thalamo-cortical circuits appear to be the principal components in the maintenance of its symptomatology.

Summary

1. A case is reported indicating that subcortical parietal lobotomy has proved effective for relief of an upper extremity phantom limb syndrome for at least fourteen months.*

2. Subcortical parietal lobotomy appears to differ in several respects from the effects sometimes encountered after frontal lobotomy. Subcortical parietal lobotomy, for example, does not lead to unfavorable personality changes, incontinence or intractable convulsive seizures, and does not permit abrupt withdrawal of narcotics.

3. It is suggested that the phantom limb syndrome, whether psychogenic or neurogenic, depends principally on contralateral parietal thalamo-cortical circuits.

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CITATION AND PRESENTATION OF THE ACADEMY MEDAL* TO EDWARDS ALBERT PARK, M.D.

ALEXANDER T. MARTIN

President, The New York Academy of Medicine

EDWARDS ALBERT PARK was born December 30, 1877, in Gloversville, N. Y., the son of a Congregational minister. He was graduated from Yale College in 1900, and received his M.D. degree from Columbia University's College of Physicians & Surgeons in 1905. An internship at Roosevelt Hospital was followed by a residency at the New York Foundling Hospital, where he made his start in studying the pathologic anatomy of pediatric problems. He held the Proudfit Fellowship in Medical Research at P. & S., and for a time an instructorship in pathology; and he also did teaching in both medicine and pediatrics.

In 1912 John Howland, who had succeeded Pirquet as head of pediatrics at Johns Hopkins, was looking for a promising student of bone growth and bone disease to take part in his projected program of investigation of rickets. It was partly at Howland's instigation, then, that Park went abroad for a year, to study under M. B. Schmidt at Marburg and to prepare himself for the important role which he was later to play in the elucidation of a number of diseases of bone and their associated disturbances of growth. On his return to the United States, the team which he found assembled in Baltimore under Howland's leadership, included a truly remarkable group—Blackfan, Gamble, Kramer, Marriott, Powers—whose influence on the flowering of American pediatrics was to prove highly enzymatic.

During the first World War Dr. Park went to France with the American Red Cross and organized—ahead of their time, and far ahead of their geographical surroundings—what we should now call child

* Presented at the Annual Meeting of The New York Academy of Medicine, January 7, 1954.

health clinics. He returned to Johns Hopkins for a short time and was then called to the chair of pediatrics at Yale, where the medical school was undergoing a drastic reorganization including the establishment of full-time clinical departments. By the time he left New Haven, six years later, he had set up a pediatric service of recognized excellence and productivity. He returned to the Johns Hopkins Medical School in 1927 as head of the Department of Pediatrics and successor of his former mentor. It was there, in Baltimore, that he spent during the next nineteen years the period of greatest fruitfulness in terms of his inspiration and activation of serious students of pediatrics. Many in this audience are grateful for having had the opportunity to be among his pupils, and all who have worked with him or have come under his influence in other ways have carried away an indelible impression of his unresting search for perfection, his intellectual integrity, his hospitality to new ideas, his inventiveness in designing hypotheses and in planning experiments, his patience in the search for facts, his critical evaluation of evidence. Many a young investigator, eager to publish his observations, has been induced by Dr. Park to demur, to gather more evidence, to try a few more controls; and later, in retrospect, has been grateful to his friendly critic for having been persuaded to keep his scientific shirt on. Fully as great as the contribution of Dr. Park's own recorded publications in science is that of his influence on his associates. His career as an educator has been Olympian. He has been honored by election as president of the American Pediatric Society and by the award of the Kober medal of the Association of American Physicians.

Now, long after his retirement from active teaching in pediatrics, Dr. Park pursues happily his studies of bones and their growing pains under the hospitable auspices of the Department of Pathology on Baltimore's Monument Street. He has thrown much light on the processes of normal growth, and on such diseases as rickets, scurvy, syphilis, chondrodystrophy, osteogenesis imperfecta, in a continuous serial of which new chapters keep coming out even when no new characters are introduced and when some of the old ones—shady ruffians like the bone lesions of congenital syphilis—have been virtually liquidated.

The New York Academy of Medicine is proud to recognize in Edwards A. Park, one of the true leaders in science of our times. In recognition thereof, I, as President of the Academy, have the pleasure and the honor to present to him the Academy Medal.

CITATION AND PRESENTATION OF THE ACADEMY PLAQUE* TO SETH MINOT MILLIKEN, M.D.

ALEXANDER T. MARTIN

President, The New York Academy of Medicine

FORTUNATE is the educational institution which numbers among its members a large group of enthusiastic and dedicated workers who labor, not for personal aggrandizement or self advancement, but for the growth and development of the institution and its reflected benefits to the community. Over the years, The New York Academy of Medicine has been blessed by the activities of many such individuals, Francis, Stearns, Purple, Jacobi, Williams, Hartwell, Miller, Goodridge—all these and many, many others have given of their energy, their thought, and their substance to the upbuilding of this Academy. Its growth has been the growth of the men who gave it being and strength.

Of such timber is Seth Minot Milliken. Graduated from the College of Physicians and Surgeons, Columbia University in 1902, he was elected a Fellow of the Academy four years later. In 1918 at the age of forty-three he was elected Treasurer of the Academy, which office he held until 1936, a span of eighteen years. These figures of themselves mean little until they are placed in their proper setting. These years saw the post World War I financial slump followed by the extreme inflationary phenomenon before the 1929 crash. This period witnessed the initiation and development of the idea of a new home to replace the building on West Forty-third Street which culminated in the opening of this edifice in 1926. This project was made possible by the concerted efforts of the Fellows and the generosity of the Carnegie Corporation

* Presented (in absentia) at the Annual Meeting of The New York Academy of Medicine, January 7, 1954.

and the Rockefeller Foundation. Further major additions to the building were made in 1932.

During these years, there were installed a full-time Director, a physician as full-time Librarian, and full-time Executive Secretaries for the Academy Standing Committees. The financial office was overhauled and the position of Comptroller established. The Academy weathered the depression of 1929 and the thirties.

Through all of these eighteen years, through all of this rapid expansion in both physical assets and organization and function, through depression and inflation, Dr. Milliken, a surgeon—not a banker, was financial officer of the Academy, responsible for its monetary affairs. Too often are these responsibilities taken for granted and go unnoticed.

Coming back to Academy affairs in 1947, Dr. Milliken served as a Trustee for five years, during which time he also served on the Committee responsible for the erection of the new library stacks, the major alterations in the Periodicals Room, and the relighting and decorating of the large Main Reading Room, all of which were completed last year.

For all of these devoted and unselfish services, covering a span of thirty-five years, effectively performed without reservation or stint, we of a later generation salute and thank him and in recognition thereof, I, as President of the Academy, have the pleasure and the honor to present the Academy Plaque on which is inscribed

"PRESENTED TO SETH MINOT MILLIKEN
IN RECOGNITION OF OUTSTANDING SERVICE TO
THE NEW YORK ACADEMY OF MEDICINE."

MEDICAL RESEARCH FORUM

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ABSTRACTS

The Rationale of Routine Omentectomy in Subtotal Gastrectomy

PAUL A. KIRSCHNER AND JOHN H. GARLOCK

From the Department of Surgery and the Laboratories of the Mount Sinai Hospital, New York, N. Y.

In the standard subtotal gastrectomy for peptic ulcer, the greater curvature of the stomach is mobilized by ligating the right and left gastroepiploic vessels and dividing the anterior leaf of the greater omentum distal to the epiploic arch. Anatomical and embryological evidence indicates that this results in a considerable degree of impairment of the vascular supply of the greater omentum, for only a meager independent supply exists in the posterior leaf. Clinical observations reveal that patients undergoing subtotal gastrectomy for carcinoma in whom the omentum is removed with the stomach commonly have a smoother convalescence than the ulcer patients in whom the omentum with impaired blood supply is allowed to remain.

Experimental impairment of the blood supply of the omentum has been carried out in dogs to an extent comparable to that occurring in the standard ulcer operation. Characteristic changes occurred at intervals of two to twenty-four days. Grossly, there is conversion of all or a major part of the filmy delicate omentum into a solid mass—heavy, soggy, and indurated—of a yellowish-brown mottled color, usually not adherent to surrounding bowel and often palpable through the abdominal wall. The cut surface is succulent in the earlier specimens, and firmer and more fibrotic later.

Microscopically, in the first week, the fat cells appear turgid, and the viability of the cell membrane is compromised. There are intercellular edema, red cell extravasation, and the appearance of young granulation tissue. In two to three weeks, more mature fibrous tissue and foreign-body giant cells appear, and the necrotic fat cells coalesce to form larger cystic spaces bounded by thin layers of fibroblastic tissue. No evidence of vascular thrombosis is present.

In general the changes are those of early inflammation and fat necrosis progressing to later fibrosis and repair.

It is postulated on the basis of these observations that omentectomy should be carried out routinely in all cases of subtotal gastrectomy. Such procedure does not deprive the patient of "the policeman of the abdomen" but rather may rid him of a noxious mass of fatty tissue undergoing necrosis, absorption, and organization. Removal is simple and bloodless as an avascular plane exists between the transverse colon and the posterior leaf. Omentectomy finds its best application in obese individuals.

The Significance of Serum Complement Levels for the Diagnosis and Prognosis of Acute and Subacute Glomerulonephritis

KURT LANGE, RUTH STRANG AND LAWRENCE B. SLOBODY

From the Departments of Medicine and Pediatrics, New York Medical College, New York

Serum complement levels are always low in acute glomerulonephritis (fifty-one cases). The lowering of complement seems to be due to an antigen-antibody reaction between the glomerular surface and the circulating antibody. Experimental evidence shows that perfusion of isolated animal kidneys with serum containing normal amounts of complement causes no reduction in complement levels. When small amounts of nephrotoxic serum are added to the perfusate, and this is circulated through the kidney, large amounts of complement are immediately removed from the perfusing serum. With healing of the disease complement returns to normal. This return may precede or follow within a few days the disappearance of all clinical signs and symptoms. Healing can occur with restitution ad integrum or with defect leaving mild degrees of albuminuria and decreased renal function.

If the disease progresses into the subacute stage complement levels remain low, although for short periods of time clinical and other laboratory signs of active disease may be absent. Cases of subacute glomerulonephritis tend to develop "acute flare-ups" under the influence of stimuli which lead to increased antibody production. All cases with persistently diminished complement levels have become either preuremic, uremic, or have died. The period of follow-up extends in some cases over four years. In addition to glomerulonephritis, only in the nephrotic syndrome, in lupus erythematosus disseminatus, in the severely edematous state of serum sickness, or massive parasitic infestations are complement values low.

Serum complement determination offers an excellent method for the differential diagnosis of hematurias and edematous conditions. A small percentage of cases of Wilms' tumor, for example, develop hematuria. Such a case, admitted to the hospital with a diagnosis of acute glomerulonephritis had normal complement levels. Shortly thereafter trauma necessitating emergency surgery revealed the presence of a Wilms' tumor. In an epidemic outbreak of glomerulonephritis in an army camp all patients, except one, had low complement values. The patient with hematuria and normal serum complement was found to have a bleeding papilloma of the bladder. Cases of sulfa-hematuria following treatment of severe tonsillitis and cases of cystopyelitis with microscopic hematuria have been diagnosed with the aid of complement determinations.

Serum Polysaccharides in Diabetic and Non-Diabetic Patients with Degenerative Vascular Disease

JAMES BERKMAN, GEORGE ROSS AND HAROLD RIFKIN
From the Laboratory and Medical Divisions, Montefiore Hospital, New York, N. Y.

In the search for factors responsible for the development of atherosclerosis, interest has centered about abnormalities of circulating lipids. However, it has been apparent that factors other than, or in addition to, disordered lipid metabolism may be decisive. In particular, there is increasing morphological and chemical evidence that a fundamental disturbance of the complex mucopolysaccharide ground substance of connective tissue precedes the subintimal deposition of lipids in the vessel wall.

Human serum contains a relatively high concentration of complex polysaccharides bound to proteins. The source, composition and function of these substances are poorly understood. However, that their distribution and concentration are altered in a wide variety of diseases has been demonstrated repeatedly. It has been suggested that these changes reflect the release into the circulation of substances derived from complex tissue carbohydrates as the result of tissue injury.

This report is based on a comparative study of certain polysaccharide components in the serum of diabetic patients and non-diabetic patients with degenerative vascular disease. We have reported previously[1] that the concentration of total non-glucosamine polysaccharides bound to serum protein and the concentration of serum glucosamine are significantly increased in diabetic patients, but only when clinically detectable degenerative vascular disease exists.

In a few non-diabetic patients with well established cerebral, coronary, renal or peripheral arteriosclerosis, the total non-glucosamine polysaccharides bound to serum protein are also elevated, and to a degree comparable to that in the diabetic group. However, in contradistinction to the pattern in diabetic patients, in the majority of non-diabetic individuals with degenerative vascular disease the values for total polysaccharides for serum glucosamine are normal or very slightly elevated.

While the quantitative interrelationship of non-glucosamine polysaccharides bound to serum protein and serum glucosamine is not known, these observations suggest that there are differences of the serum glycoprotein patterns in the categories of patients studied. The possible significance of this observation will be discussed.

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Pitfall in the Diagnostic Use of Radioactive Iodine; Hyperthyroid Values in Non-Toxic Patients (Preliminary Report)

SOLOMON SILVER, STEPHEN B. YOHALEM AND ROBERT A. NEWBURGER

From the Department of Medicine and the Laboratories of The Mount Sinai Hospital, New York, N. Y.

Thyroidal uptake of radioactive iodine (I-131), carrier-free, after tracer doses has become an important diagnostic aid in thyroid disorders. In some clinics it has replaced the determination of the basal metabolic rate (B.M.R.) as the primary laboratory aid in the separation of hyperthyroid and euthyroid patients.

It is not our purpose in this communication to deprecate the usefulness of uptake studies or any other laboratory test in the diagnosis of hyperthyroidism. We are strongly of the opinion that only a full and careful clinical study can establish the diagnosis of hyperthyroidism and that all that we can expect from any laboratory test is a result which we must then interpret in the light of all the other available data, clinical and laboratory. Any attempt to replace the clinician by a laboratory test is predestined to failure.

In 1950[1] and again in 1952[2] we reported on the value of the determination of the protein-bound I-131 levels in the blood plasma at 72 hours after the tracer dose. Values in excess of 0.3 per cent of the tracer dose per liter of plasma were considered "hyperthyroids." We are convinced that this is the *best single test using I-131* in the diagnosis of hyperthyroidism and will often give diagnostic information when the uptake studies alone are equivocal or misleading.

We have encountered a group of patients in whom the I-131 studies were at such variance with the clinical picture and other laboratory data that it became clear that the I-131 studies, which were clearly in the range considered characteristic of hyperthyroidism, were discordant. These "false hyperthyroid" values occurred both with uptake and protein-bound plasma I-131 levels, but were more frequent in the former.

So far as we can determine no systematic study of this phenomenon has been made, but isolated reference to its occurrence can be found in the literature dating back to the earliest work with I-131. Radioactive tracer values usually considered diagnostic of hyperthyroidism have been reported after clinical cure of the hyperthyroid state by I-131 or surgery, in endemic and sporadic goiter, in goitrous cretinism and in experimental goiter induced by various goitrogens. We have observed them in apparently normal patients, after control of hyperthyroidism with I-131 and in the period following withdrawal of thyroid extract and iodides.

We shall present data on a group of patients who were clearly not hyperthyroid as judged by experienced clinicians. The B.M.R. and the protein-bound serum iodine values confirmed the clinical impression. However, the thyroidal uptake at 24 hours after the tracer dose was over 55 per cent and in some cases the protein-bound plasma I-131 levels were over 0.3 per cent of the administered dose per liter.

The realization that euthyroid and even hypothyroid individuals when tested with I-131 can give findings generally accepted as diagnostic of active hyperthyroidism will prevent unnecessary treatment. It will also avoid further therapy with I-131 after a clinical cure has been obtained and thereby reduce the incidence of post-treatment myxedema.

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*Cardiac Pain in Man: Blocking Effect of Ethyl Chloride Spray on the Angina of Ergonovine**

ISIDORE STEIN, SEYMOUR H. RINZLER, HYMAN BAKST, JOSEPH WEINSTEIN, ROBERT GITTLER AND JANET TRAVELL

From the Veterans Administration, Regional Office, Brooklyn, N. Y., the Cardiovascular Research Unit, Beth Israel Hospital, New York, N. Y., and the Department of Pharmacology, Cornell University Medical College, New York, N. Y.

We have used intravenous ergonovine maleate as a test for coronary insufficiency 260 times in 169 patients with chest pain and a normal resting electrocardiogram. Seventy-six of these patients gave a typical history of angina of effort and in sixty-two (82 per cent) the ergonovine test was positive, as evidenced by appearance of chest pain and/or electrocardiographic changes (depression of the S-T segment and/or inversion of the T wave). In all but one of the sixty patients who showed electrocardiographic changes after ergonovine, chest pain also occurred. Two patients experienced chest pain alone without electrocardiographic alterations. Changes in blood pressure and pulse rate after ergonovine were minimal. In seeking an objective method for the diagnosis of coronary insufficiency which would obviate the patient's experiencing pain, an investigation was undertaken to study the blocking effect of ethyl chloride spray on the cardiac pain and on the electrocardiographic changes induced by ergonovine in suitable patients. The choice of ethyl chloride spray was based on reports by Rinzler and Travell of the effectiveness of the spray in blocking the somatic component of cardiac pain when this occurs in acute myocardial infarction, angina pectoris and the shoulder-hand syndrome accompanying coronary insufficiency.

Thirty-six tests were done on seven patients (forty-four to seventy years, five males and two females) who had effort angina but a normal resting electrocardiogram, and who on intravenous administration of ergonovine maleate (0.1 to 0.4 mg.) promptly developed an abnormal electrocardiogram and also pain in the chest, shoulder, arm or neck similar to that induced by effort. Intravenous injection of physiologic saline in the same volume produced neither pain nor electrocardiographic changes in any of the seven patients. Nitroglycerin (0.4 or 0.6 mg.) given sublingually prior to ergonovine prevented both pain and electrocardiographic changes in five of the seven patients. When ethyl chloride was applied to the potential pain areas just *before* ergonovine was injected, it prevented the predicted painful response to ergonovine in four of seven patients, but not the changes in the electrocardiogram. When ethyl chloride spray was applied *after* ergonovine had been injected and pain had appeared, the spraying relieved pain completely in four of six patients and partially in the two others, despite persistence of the electrocardiographic changes until nitroglycerin was given.

This study affords additional evidence for the previously reported efficacy of ethyl chloride spray for the relief of the somatic component of cardiac pain. Furthermore, modification of our usual ergonovine test by prior application of ethyl chloride spray provides a pharmacologically controlled stress test for coronary insufficiency which has the following advantages: 1) It eliminates the associated pain in a large proportion of patients; 2) tachycardia does not usually occur to confuse the electrocardiographic interpretation; 3) the test can be done on the group of patients who for reasons other than cardiac cannot exercise; and 4) the positive electrocardiographic changes may be quickly reversed to normal by nitroglycerin.

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*The Application of Quantitative Paper Chromatographic Methods to the Study of Human Serum Phosphatides in Normal and Pathologic States**

JACOB KREAM AND MENARD M. GERTLER

From the Department of Medicine, Home for Aged and Infirm Hebrews, New York, N. Y.

Recent observations appear to indicate that there is an association between human atherosclerosis and gross changes in serum phosphatides. Since this lipid fraction is heterogeneous it would be desirable and of interest to distinguish the differential changes, if any, in the individual phosphatide components. Quantitative paper chromatographic methods offered interesting possibilities in that they could be adapted, both to the quantitative and qualitative microanalysis of serum phosphatide components such as choline, serine and ethanolamine containing types. Such methods have been developed in our laboratory during the past year permitting direct phosphatide analysis on small samples of serum. Basically the method consists of (a) extraction of the phosphatide components from serum, (b) hydrolysis of the phosphatide extracts, and (c) separation of the nitrogenous components (choline, serine and ethanolamine) of the resulting hydrolysate by means of paper partition chromatography and their quantitative estimation by means of quantitative colorimetry.

Data will be presented from (a) normal individuals of various age groups, (b) individuals who have clinical atherosclerosis and (c) correlative studies relating *Sf* molecules with the afore-mentioned phosphatidyl bases.

In all, over seventy analyses have been performed. The preliminary results reveal different ratios of choline to serine and ethanolamine in the various disease states. The significance of these results in maintaining the cholesterol in colloidal suspension will be discussed.

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Further Studies of the Etiologic Agent of Pemphigus Vulgaris

ARTHUR W. GRACE

Division of Dermatology and Syphilology, Department of Medicine, College of Medicine, State University of New York at New York City, Brooklyn, N. Y.

The following materials, pemphigus, erythema multiforme bullosum and normal in origin, were inoculated intracerebrally in mice irradiated with 400 r x-ray, 1.4 mm. copper HVL: 23 blister fluids, 40 blood sera and 6 cerebrospinal fluids. These experiments showed that blister fluids arising spontaneously in pemphigus and erythema multiforme bullosum are more lethal to mice than those induced by the application of a vesicant to intact skin; also, that blister fluids from pemphigus and erythema multiforme bullosum patients, and blood sera and cerebrospinal fluids from pemphigus patients, are more likely to produce a high mortality in mice, and marked pathologic change in mouse brains, when those patients are seriously, rather than mildly ill. These studies produced 3 strains of transmissible agent; the properties of one have already been reported.[1-4] Another series of experiments was performed in

which mice were prepared, before intracerebral inoculation, by irradiation with 400 r x-ray, 0.6 mm. copper HVL; no irradiation deaths occurred. Inocula consisted of 1 pemphigus blister fluid, 1 pemphigus autopsy spleen and 3 normal mouse brains. Transmissible agents were obtained from both pemphigus materials and maintained serially for sixteen and seventeen passages respectively. The pathologic changes in mouse brains were identical in both strains and with those produced by the strains already reported.[1-4] No transmissible agent was obtained from the three normal mouse brains. Pleuropneumonia-like organisms[5] were not obtained on culture of four pemphigus blister fluids or of infective mouse brains. Establishment of the transmissible agent as the cause of pemphigus cannot be attempted by human inoculation. Accordingly, the presence of neutralizing antibodies was sought in thirty blood sera, derived from fourteen pemphigus patients and twelve normal persons, by a procedure whereby a relative index of the neutralizing power of each serum can be obtained; a smaller index indicates a higher relative neutralizing power than does a larger one. An index less than 50 was found in three normals and eight pemphigus patients, and more than 50, in eleven normals and eight pemphigus patients. Four of the pemphigus patients showing the smaller index were ambulatory, and none seriously ill. None of the pemphigus patients showing the higher index were ambulatory and five were seriously ill; five of the group with the higher index died without remission, two and ten days, and three, five and six months, respectively, after serum was drawn. Another experiment, performed in a single individual, showed that the index became smaller with clinical improvement and larger with clinical deterioration. The agent is regarded by the author as the cause of pemphigus, and probably resides on the skin; it is totally unlike any spontaneous mouse virus.[6-11] Consideration of its nature and origin must include the existence, in pemphigus blister fluid, of two types of particle, one, measuring 250 to 300 millimicrons and another, 20 to 75 millimicrons in diameter; the lack of contagiousness of pemphigus; the average, and youngest, ages of the 118 pemphigus patients in this study, of 54.7 and 24 years, respectively; the high incidence, 66.4 per cent, of Jewish patients in the same group.

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The Effect of Hypoxia Upon Pulmonary Vessels

ARTHUR A. SIEBENS, LT. (MC.) USNR,
RALPH E. SMITH, LT. (MC.) USNR
AND CLIFFORD F. STOREY, CAPT. (MC.) USN

Although factors which regulate systemic blood pressure and flow have been well established, relatively little is known concerning the control of the lesser circulation. The presence of a low oxygen tension in inspired air, however, has been demonstrated to be an effective stimulus; acute hypoxia in man as well as in animals induces a prompt elevation of pulmonary artery pressure.

There exists considerable divergence of opinion as to the mechanism for this pressor response. On the one hand are those who have found that hypoxia in animals produces an increase in pulmonary blood flow to which the rise in pressure may be attributed; on the other are experiments in which the vascular resistance of a lung subjected to low oxygen breathing has been deduced to increase in comparison to that of its mate ventilated with normal or high oxygen concentrations. Attempts to distinguish between the roles of flow and resistance under hypoxic conditions in man have been unsuccessful largely because of difficulties in achieving the steady state essential to calculating cardiac output by the Fick equation.

The present report concerns four patients for whom reliable calculations of oxygen consumption and pulmonary blood flow show a fall with hypoxia coincidentally with a rise in pulmonary artery pressure. These patients were studied at rest, at exercise while breathing room air, and at exercise while breathing a gas mixture adequate for lowering oxyhemoglobin saturation of arterial blood to approximately 80 per cent. Each of the four was hospitalized for bilateral bronchiectasis. One was catheterized preoperatively, two after excision of disease on one side, and one after completion of bilateral segmental resections. The selection of patients with an attenuated vascular cross sectional area and the use of exercise for increasing flow were designed, according to the provisions of Poiseuille's law, to favor the detection of pressure changes due to resistance changes.* Measurements of cardiac output by the Fick principle were made after a reasonably "steady state" had been achieved.

Pulmonary vascular resistance was found to fall as blood flow increased with exercise in the well saturated patient. In contrast, pulmonary resistance increased sharply during exercise on low oxygen. It is concluded that acute hypoxia produced pulmonary vasoconstriction in these four patients.

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* $P = (8L/\pi r^4) \cdot vI$; where P is the pressure drop between two points in a hydraulic system, L is the length of the tube, v is the viscosity of fluid, I is the volume flow, and r is the radius. Although this equation holds only where flow is laminar and the fluid is homogeneous, it was assumed that introducing turbulence and non-homogeneity as in the lesser circulation does not destroy the curvilinear relationship between P and r. This relationship is such that a unitary decrement in r is associated with larger increments in P when r is small, as following pulmonary resection, and I large, as during exercise.

Furadantin in the Treatment of Infections Due to B.proteus

CHARLES E. FRIEDGOOD AND CHARLES B. RIPSTEIN
Department of Surgery, Maimonides Hospital of Brooklyn and State University of New York, College of Medicine at New York City

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A group of 108 patients including eight infants with pyuria due to either a cystitis or pyelonephritis were selected in whom the infecting organism was completely resistant to all other intensive antibiotic therapy. In the majority of the cases the organism was B. proteus. The patients were then placed on divided doses of oral Furadantin therapy four times a day. The acute cases showed a remarkable response to the drug with approximately 85 per cent cures within one week. The chronic group of patients, many of whom had symptoms for over a year, had a lower cure rate of approximately 55 per cent sterile urine cultures. The only side reaction noted was some nausea which could be controlled by lowering the dose. There was no evidence of any other toxicity or sensitization.

Six cases of B. proteus septicemia which were completely refractory to all other antibiotic therapy were treated successfully with Furadantin. Two cases of B. proteus empyema and sixteen cases of B. proteus wound infections were also sterilized by the local use of Furadantin. Laboratory data on blood cell and chemistry studies will be presented along with bacteriological changes.

These results indicate that Furadantin is a safe and effective drug for the treatment of various types of infections due to antibiotic resistant organisms.

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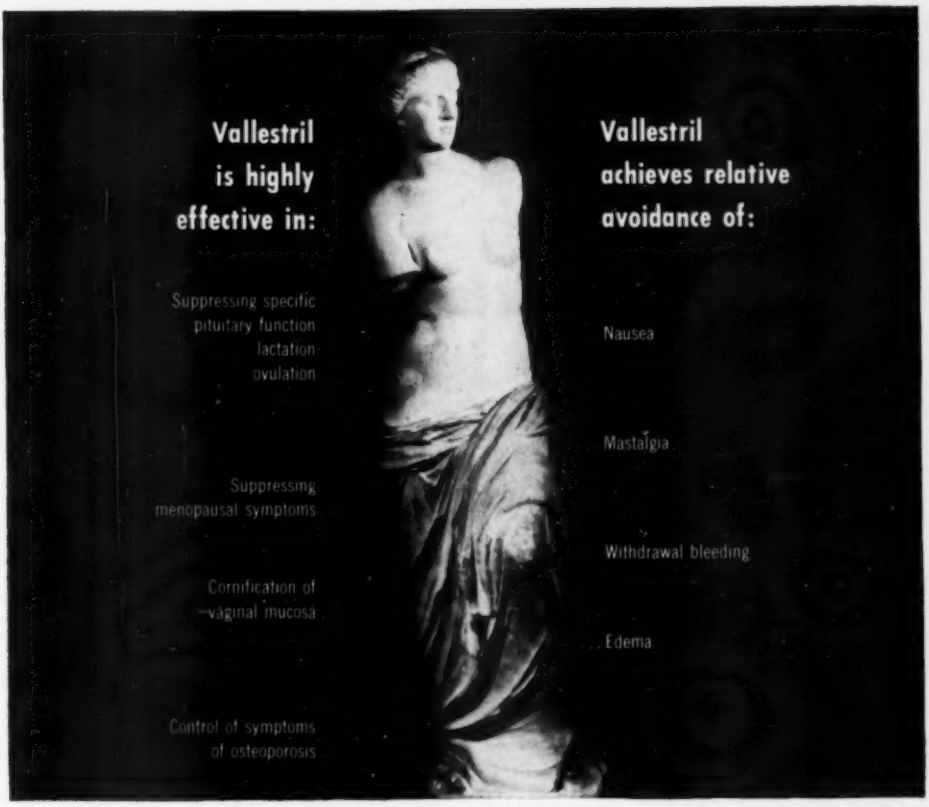

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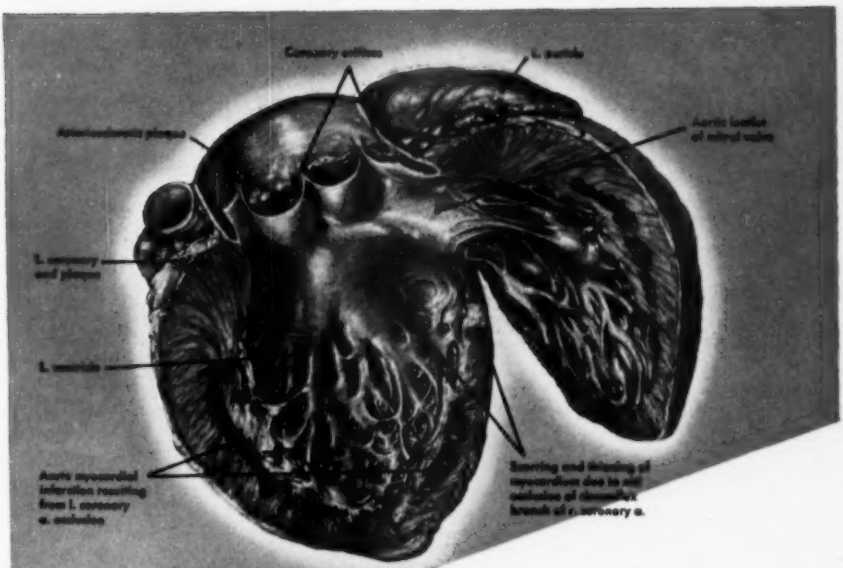
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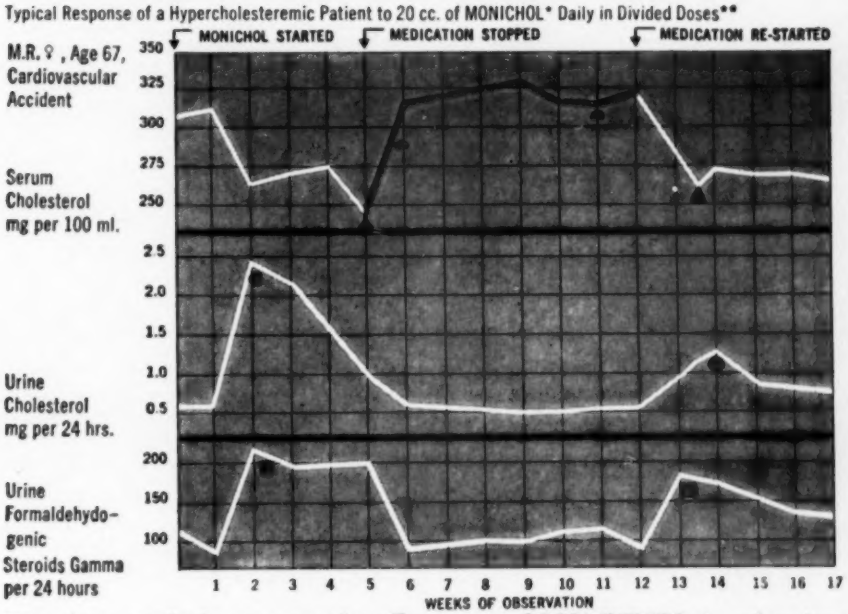

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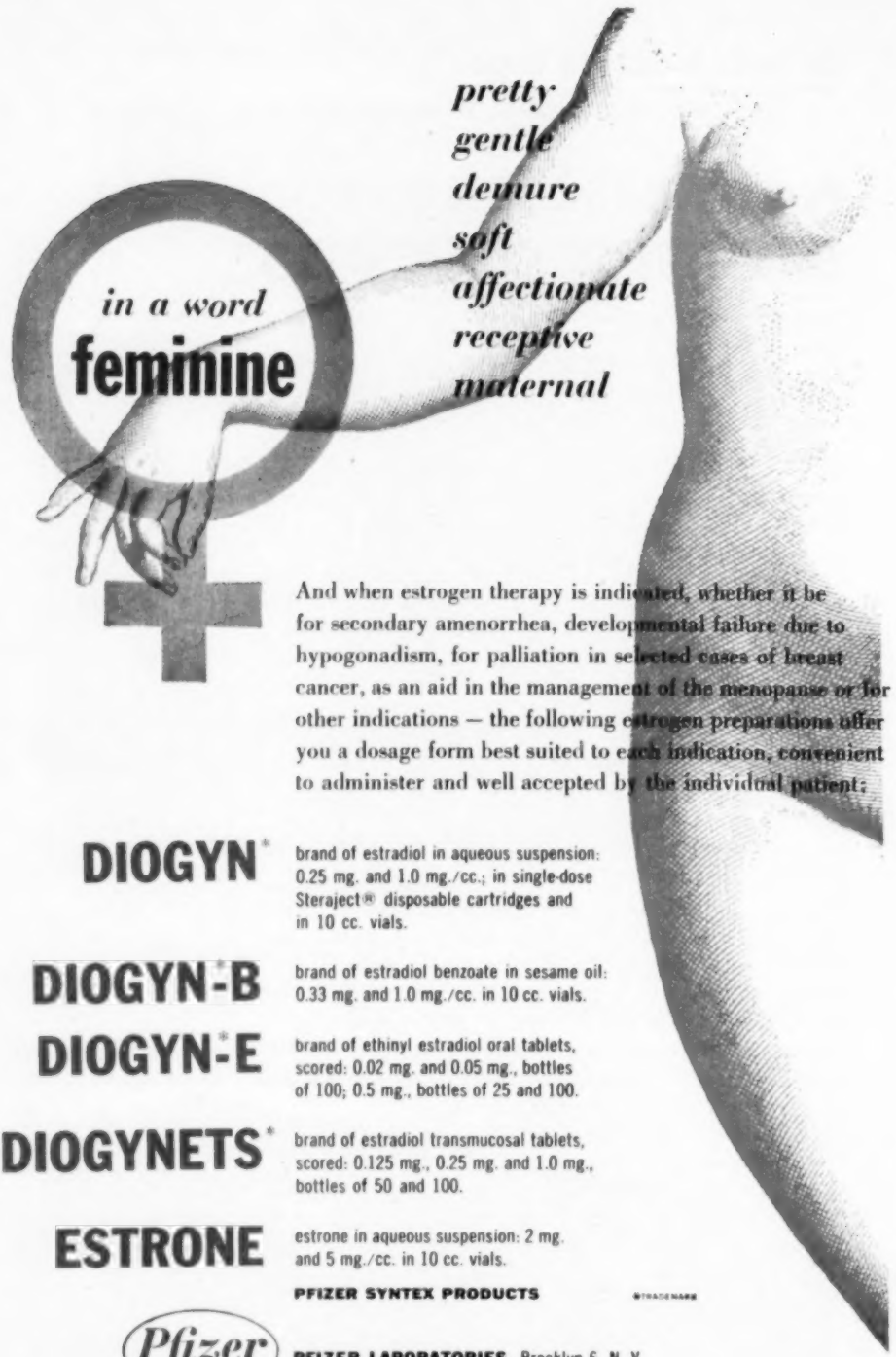

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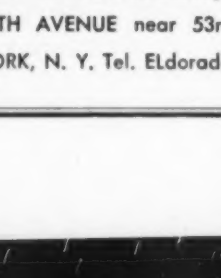

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True broad-spectrum action

"Terramycin appears to have [a] most widespread effective range...."[1]

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"Terramycin administered orally was absorbed rapidly with the appearance of antibacterial activity in the serum within 1 hour of administration."[2]

Promptly effective

Many "patients...improved rapidly"[3] with return of temperature to normal often noted within twenty-four hours.

Well tolerated

"Terramycin is generally well tolerated...."[4]

Terramycin®

Brand of oxytetracycline

1. Cowart, E. C., Jr.: Mississippi Doctor 29: 278 (April) 1952.
2. Sayer, R. J., et al.: Am. J. M. Sc. 221: 256 (March) 1951.
3. Kuzell, W. C.: New York State J. Med. 50: 2173 (Sept. 15) 1950.
4. Trafton, H. M., and Lind, H. E.: J. Urol. 69: 315 (Feb.) 1953.

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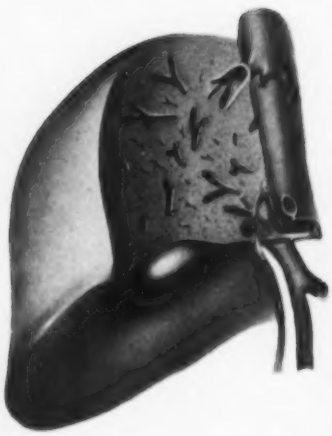
protect the liver...



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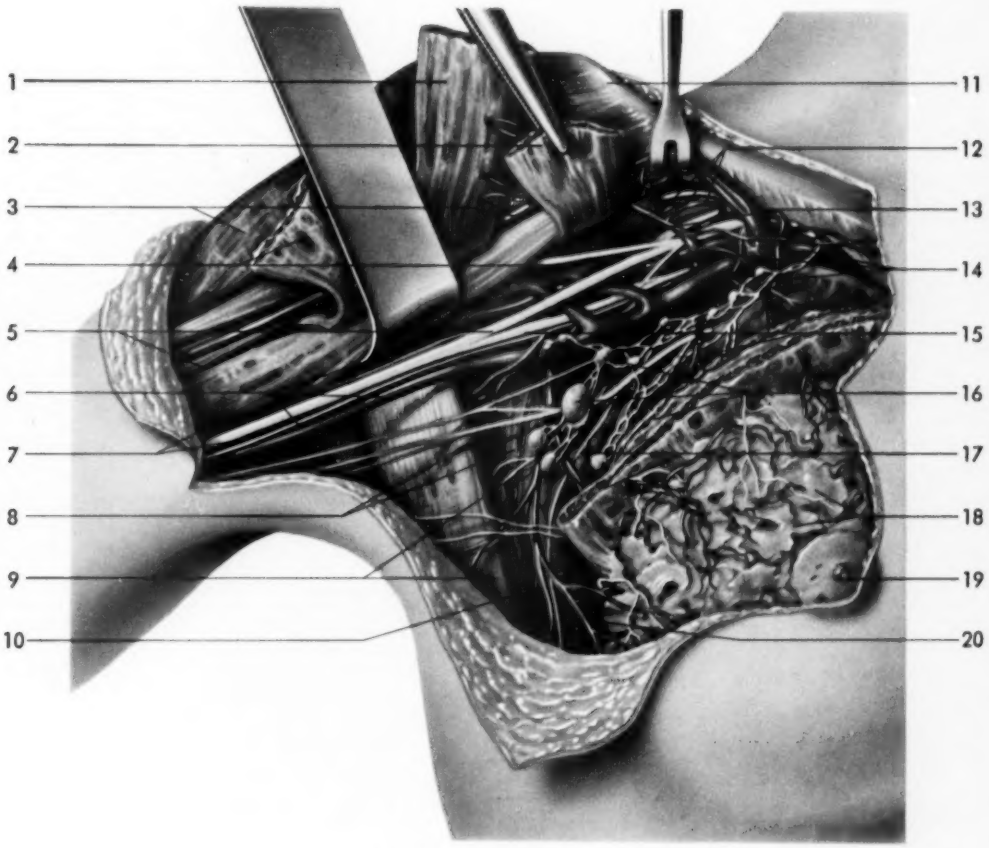
The Axillary Region



1 Pectoralis major muscle
2 Pectoralis minor muscle
3 Deltoid muscle; cephalic vein
4 Pectoralis major muscle; musculocutaneous nerve
5 Long head of biceps brachii muscle; lateral branch of median nerve
6 Brachial artery and vein; ulnar nerve
7 Short head of biceps brachii muscle; median nerve
8 Intercostobrachial nerve; subscapularis muscle
9 Thoracodorsal nerve; latissimus dorsi muscle
10 Branch of thoracodorsal artery
11 Acromial extremity of clavicle
12 Suprascapular artery, vein and nerve
13 Thoracoacromial artery
14 Axillary artery and vein; subclavian lymphatic trunk
15 Medial branch of median nerve; lateral thoracic artery
16 Axillary lymph nodes; pectoralis major muscle
17 Long thoracic nerve; pectoralis major muscle
18 Lobes of breast
19 Papilla of breast
20 Thoracoepigastric vein

This is one of a series of paintings for Lederle by Paul Peck, illustrating the anatomy of various organs and tissues of the body which are frequently attacked by infection, where Aureomycin may prove useful.

Lederle

Aureomycin*

CHLORTETRACYCLINE

produces rapid response in

infections of the soft tissues

caused by staphylococci, streptococci,

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of

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